DISSERTATION ON

‘‘NEURODEVELOPMENTAL SEQUELAE OF NEONATAL SEIZURES IN NEWBORN”

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CERTIFICATE

This is to certify that this dissertation entitled **"NEURODEVELOPMENTAL SEQUELAE OF SEIZURES IN NEWBORN"** is a bonafide work done by **Dr. S.SHIVA SHANKARAN M.D.,** Post graduate in the Institute of Social Paediatrics, Stanley Medical College, Chennai, during the academic year 2009-2012.

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DECLARATION

I solemnly declare that the dissertation entitled **“NEURODEVELOPMENTAL SEQUELAE OF SEIZURES IN NEWBORN"** was done by me at Institute of Social Pediatrics, Government Stanley Medical College and Hospital during 2009- 2012 under the guidance and supervision of Professor **G.KARUNAKARAN M.D., Dch.** The dissertation is submitted to the Tamil Nadu Dr.MGR Medical University towards the partial fulfillment of requirements for the award of M.D.DEGREE (BRANCH – VII) in Pediatric medicine.

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CONTENTS

INTRODUCTION

INTRODUCTION

Clinical seizures are defined as paroxysmal alteration in neurological function i.e. behavioural, motor and/or autonomic function. Newborn period is the time when the incidence of seizures is the highest, yet their clinical recognition is difficult, therefore true incidence of neonatal seizures is difficult to determine.[1] Its incidence varies from 1-5 per 1000 live births.[2-6] Neonatal seizures are very common in the first weeks of life. Clinical features of neonatal seizures are different from those in adults.[7] Neonatal seizures are distinctive clinical manifestation of neurological dysfunction in the newborn.[8] Newborn infants with seizures are at risk for neonatal death and survivors are at risk for neurological impairment, developmental delay, and later epilepsy. [8-12]

Despite increasingly sophisticated neonatal intensive care, neonatal seizures remains a challenge.[8-13] Neonatal seizures can be due to various causes like hypoxic-ischemic encephalopathy, intracranial hemorrhage, meningitis, hypoglycemia, hypocalcemia, congenital malformation, etc.[1] The most important factor that predicts their outcome is the underlying etiology.[14] Patients with hypoxic encephalopathy (HIE), intraventricular hemorrhage (IVH) and neuronal migration disorders (NMD) are reported to have the worst prognosis. Etiologic profile of neonatal seizures is also changing over the years due to advanced development in obstetric and neonatal management that have changed the spectrum of insults to which the immature brain is exposed.[15-18]

The mortality of infants developing seizures during the neonatal period has shown a decreasing trend over time. In earlier studies, the mortality was as

high as 40%, but decreased in subsequent reports to 20%. [8,9,19-22] As opposed to this increase in survival, the prevalence of long-term neurodevelopmental sequelae in survivors has remained unchanged at 30%.[8,19,23] However, neonatal seizures remain an important predictor of future neurological complications. [6,20] In addition it may be associated with other permanent neurological disorders such as mental retardation and cerebral palsy. The occurrence of epilepsy after neonatal seizures varies in frequency as shown in previous studies from 3.5 to 56% according to sample selection.[12]

The aims of the current study were to assess the neurodevelopmental outcome of neonatal seizures and prognostic indicators of outcome (like onset of seizure, type of seizure, EEG changes, etc) for infants surviving neonatal seizures.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DEFINITION

" Clinical seizures" may be defined as paroxysmal alterations of neurologic function, including behavioural, motor, and/or autonomic changes.

PATHOPHYSIOLOGY

Seizures are the most common and distinctive clinical manifestation of neurologic dysfunction in the newborn infant[8]. Neonatal seizures often herald potentially devastating forms of brain injury. Decreased seizure threshold in the newborn period reflects the undergoing active developmental process in the immature brain. The newborn brain has transient overdevelopment of excitatory system when compared to inhibitory system, for example there is a transient over expression of Glutamate receptors and relative paucity of glutamate reuptake transporters. These two factors causes prolonged and intense contact of glutamate with the post synaptic receptors. Moreover these immature glutamate receptors are more permeable to cationic influx, facilitating membrane depolarisation and seizure activation. In contrast, inhibitory GABA ion channels are under expressed in immature brain. In certain areas of brain these GABA ion channels tend to depolarize rather than hyperpolarizing. In addition to these cellular effect, there are other mechanism for seizures in newborn; eg: 'differential development of neural system' where there is relatively advanced development of excitatory projections in substantia nigra, compared to inhibitory pathways; so it act as an amplifier rather than inhibitor of epileptic discharges, predisposing to neonatal seizures.[24]

INCIDENCE OF NEONATAL SEIZURE

Incidence of neonatal seizures varies widely across studies. In earlier reports, seizures occurred in up to 3/1,000 full-term infants and up to 60/1,000 premature infants. National Collaborative Perinatal Project reported an incidence of 5 per 1000 live births between 1959-1966.[25] The national Neonatal – Perinatal Database of India that collated information from 18 centres across the country in the year 2002-2003 had reported an incidence of 1.[26]

SEIZURE MIMICS

Neonatal seizures differ considerably from seizures observed in older children, principally because the immature brain is less capable of propagating generalized or organized electrical discharges. Continuous video-EEG monitoring has demonstrated a number of important facts about seizures in the newborn. First, nonepileptic mimics of clinical seizures are common in the newborn. These seizure-like behaviour patterns may occur in the normal newborn (e.g., non-nutritive sucking) and nonepileptic paroxysmal clinical changes are common in encephalopathic newborns. Differentiation of nonepileptic movement from seizure is difficult in newborns. Particularly clonic seizure is difficult to differentiate from jitteriness. Following clinical observation helps to resolve the difference.[27]

- Jitteriness is not accompanied by abnormal eye movements.
- Jitteriness may be spontaneous or stimulus sensitive.
- The flexion and extension phases of the tremor are equal in amplitude compared to the unequal phases observed with clonic seizure movements.

- Jitteriness may be stopped by passive flexion or repositioning of the affected body part.

Benign neonatal sleep myoclonus occurs during active sleep in healthy preterm and in some term babies. Myoclonus may be florid and consist of either bilateral synchronus or asynchronus or asymmetric movements that are not stimulus sensitive. These myoclonus ceases on arousal from sleep. EEG shows no epileptiform activity or background abnormalities. Benign neonatal sleep myoclonus tend to resolve over months[28,29]

CLASSIFICATION

Clinical seizure types may be categorized broadly into four groups:[8,24]

Subtle seizure: They are called subtle, because the clinical manifestation are mild and tend to be missed frequently. Subtle seizures include a broad spectrum of behavioural phenomena, occurring in isolation or in combination. They are the commonest type and account for 50% of cases.

Common manifestation of subtle seizures are:-

Ocular: tonic horizontal deviation of eyes or sustained eye opening with ocular fixation or cycled fluttering.

Oral- facial- lingual movements: chewing, tongue thrusting, lip smacking, etc.

Limb movements: cycling, paddling, boxing jabs, etc.

Autonomic phenomenon: tachycardia or bradycardia.

Apnea: this is a rare manifestation of seizure. Apnea due to seizure activity may have accelerated heart rate or normal heart rate when evaluated for 20 seconds. Bradycardia may occur later secondary to hypoxia.

The association between clinical and EEG events is variable, most subtle seizures are not associated with EEG seizures. Based on their inconsistent association with EEG seizures, as well as their poor response to conventional anticonvulsants, many consider these subtle seizures to be nonepileptic "brainstem release phenomena."

Clonic seizure: They are stereotypic and repetitive biphasic movements with a fast contraction phase and a slower relaxation phase. The rhythm of clonic seizures tends to be slower in the newborn than in older children. Clonic seizures may be unifocal, multifocal, or generalized. Clonic seizures that remain unifocal are usually not associated with loss of consciousness. The most common cause for clonic seizures that remain unifocal is neonatal stroke. These seizures are commonly associated with EEG changes.

Tonic seizures: This type of seizure refers to sustained flexion or extension of axial or appendicular group of muscles. Tonic seizures may be generalized or focal and may mimic decorticate or decerebrate posturing. They are common in premature infants with major neurologic dysfunction or severe intraventricular hemorrhage. The background EEG pattern tend to have multifocal or generalized voltage depression and undifferentiated frequencies and in some cases, a markedly abnormal burst suppression pattern. Overall, the prognosis of tonic seizure is very poor.

Myoclonic seizure: This type of seizure manifest as single or multiple, lightening fast jerks of upper limb or lower limb. This type of seizure is differentiated from clonic seizure by rapid jerks, absence of slow return and predilection for flexor groups of muscle. EEG changes include burst suppression pattern, focal sharp waves and hypsarrhythmia. Myoclonic seizures are usually associated with a poor long-term outcome.

CAUSES OF NEONATAL SEIZURE

Once neonatal seizure is suspected , focus should be on the exclusion of rapidly correctable and potentially injurious conditions, including hypoglycemia, hypocalcemia, hypomagnesemia, among others. Thus, when neonatal seizures occur, immediate attention must be directed towards the identification of an underlying etiology to permit rapid and appropriate intervention and meaningful prediction of outcome.[30] Following are the causes of neonatal seizures:

- Hypoxic ischemic encephalopathy
- Intracranial hemorrhage
- Central nervous system infections
- Metabolic disturbances
- Cerebral dysgenesis
- Unknown
- Epileptic syndromes

Hypoxic- ischemic Encephalopathy (HIE): The leading cause of neonatal seizure is cerebral hypoxic-ischemia, which may occur in antenatal, intrapartum or neonatal period. Perinatal asphyxia is implicated in 25% to 40% of neonatal

seizure. Most seizures (50%-65%) due to HIE, manifest within 12 hours, remaining manifest within 24- 48 hours of age. The seizure onset in each case is likely influenced by the severity, duration, and onset of the intrauterine asphyxial insult. It is likely that more severe insults are followed by earlier onset seizures, but this is not firmly established. Subtle seizures are most common type of seizure following HIE.

Intracranial hemorrhage: Approximately 10% of neonatal seizure is caused by intracranial hemorrhage. The location of hemorrhage and clinical features varies with the gestational age. Primary subarachnoid hemorrhage is most commonly seen in term newborns. It commonly occurs after prolonged labour. Seizures are usually focal or multifocal, occurring on the second day of life. Infants appear relatively well between seizures. Infants with seizures associated with primary subarachnoid hemorrhage have a good long term outcome in 90% of cases. Posthemorrhagic seizures in preterm infants have different features and a more ominous prognosis. Seizures are usually associated with severe IVH or its complications, periventricular hemorrhagic infarction. Seizures due to severe IVH usually occur within 3 days of life in sick preterm babies. The seizures are usually generalised tonic seizures. Seizures associated with periventricular hemorrhagic infarction tend to occur after the 3rd day of life.

Central nervous system infection: Infecions from a variety of agents, including viral, bacterial, or others like toxoplasmosis, may have neonatal seizure as a prominent part of their presentation. Intrauterine infection due to toxoplasmosis or cytomegalo virus, that are severe enough to produce neonatal seizure usually manifest within 3 days of life. Viral infections like herpes simplex virus(HSV)

type-2 , acquired during intrapartum period manifest neonatal seizure within first day of life, whereas HSV-1 have a delayed presentation. Bacterial meningitis due to Group B streptococcal meningitis may also have biphasic presentation. Mechanism of seizure in meningitis may be through direct cerebritis or vaso-occlusive injury with secondary seizures.

Metabolic disturbances: Two types of metabolic disturbances may result in neonatal seizures.

1) Transient metabolic disturbances: These include hypoglycemia, hypocalcemia, hypomagnesemia, and hyponatremia.

2) Inborn error of metabolism: These are uncommon cause of neonatal seizure. Certain conditions more likely to be associated with neonatal seizure include non-ketotic hyperglycinemia, pyridoxine dependency, sulphate oxidase deficiency, glutaric aciduria type-II, urea cycle defect. Most common diagnostic abnormalities associated with these conditions include metabolic acidosis, hyperammonemia, hypoglycemia, and ketosis. Recognition of these conditions are important because some metabolic forms are transient that resolve over time e.g. Non-ketotic hyperglycinemia. Secondly some of the conditions are treatable e.g. Pyridoxine dependent seizure. In both the conditions early diagnosis and management may prevent or limit brain damage.

Cerebral dysgenesis: number of dysgenetic cerebral lesions may be associated with neonatal seizures. Conditions most commonly associated are neuronal migration disorders (lissencephaly, heterotopias) or disorders of neuronal organization (polymicrogyria).

Unknown etiology : approximately 10% of neonatal seizures are due to unknown etiology.[24]

Epileptic syndromes in the newborn infant: There are two benign and three malignant epileptic syndromes presenting with seizures in the newborn infant.

Benign condition are i) benign familial neonatal seizure

ii) benign idiopathic seizure.

Three malignant conditions are

i) neonatal myoclonic encephalopathy

ii) Ohtahara syndrome

iii) Migrating partial seizures of infancy (Coppola syndrome).

All three conditions carry worst prognosis.

DIAGNOSIS

The evaluation should start with a careful history of pregnancy, labour and delivery, and family, followed by a detailed clinical examination for signs of dysmorphism, trauma, skin lesions, and unusual odours. The neurologic examination should include a careful and accurate clinical description of the seizure features, the infant's mental status, and cranial nerve examination as well as interictal movements, muscle tone, and deep tendon and primitive reflexes. Certain clinical signs may suggest specific etiologies and may facilitate a more rapid etiologic diagnosis.

Laboratory investigation

Investigation that is done in all newborns with neonatal seizure are blood glucose, hematocrit, serum electrolytes, serum bilirubin if newborn is clinically jaundiced. CSF analysis should be done in all cases as seizures may be the first sign of meningitis and also it may be coexisting, when other causes are identified. CSF analysis may be withheld when there is cardiopulmonary instability or severe birth asphyxia. Cranial ultrasound and EEG are routinely done for all cases of neonatal seizure. Ideally an EEG study should be recorded as soon as a seizure is suspected and preferably not later than 24 hours after. If such an EEG is normal, particularly if a suspected clinical event is captured during the EEG recording, then subsequent EEGs are only indicated if the clinical spells keep recurring. EEG should be performed for at least 1 hour.[31] Interictal EEG is useful for long term prognosis of neonates with seizure. An ABG should be performed when Inborn error of metabolism is strongly suspected. Specific investigation are needed when neonatal seizures are not responding to usual line of management. These include neuroimaging CT/MRI , screening for congenital infections (TORCH), inborn error of metabolism. Ultra sonogram of the cranium is an excellent tool to diagnose intraventricular hemorrhage and parenchymal hemorrhage.

TREATMENT

Initial management includes stabilization of airway, breathing and circulation and temperature. Oxygen should be delivered through mask, IV access and blood should be collected for blood glucose and other investigations. A brief history and rapid clinical examination should be done.

i) Hypoglycemia is corrected with 2 ml/kg of 10% dextrose bolus through IV followed by 6-8 mg/kg/min infusion.

ii) Hypocalcemia is corrected after ruling out hypoglycemia with bolus of 2 ml/kg of 10% calcium gluconate over ten to fifteen minutes under strict cardiac monitoring followed by 8 ml/kg/day for 3 days if investigation shows hypocalcemia. If still seizure persist after correction of hypocalcemia 50% magnesium sulphate at dose of 0.25 ml/kg is given as i.m injection. When seizure persists even after correction of hypoglycemia and hypocalcemia antiepileptics are considered.

iii) Phenobarbitone : It is the drug of choice in neonatal seizure. A loading dose of 20 mg/kg bolus is given under cardio respiratory monitoring over 20 minutes, rate of administration should not be more than 1mg/kg/min. If seizure still persists, a repeat dose of 10mg/kg is given every 30 minutes till 40mg/kg dose is reached. Maintenance dose of 3-5 mg/kg/day in 2 divided doses is started 12 hours after the loading dose.

iv) Phenytoin is considered when seizures are not controlled with phenobarbitone. It is given as a loading dose of 20 mg/kg over 20 minutes under cardiac monitoring. Repeat dose 10 mg/kg is given if seizure is not controlled. This is followed by maintenance dose of 3-5 mg/kg/day in 2 - 4 divided dose. It is preferably discontinued before the infant is discharged. Fosphenytoin, a prodrug of phenytoin causes less degree of hypotension and cardiac arrhythmia when compared with phenytoin. 1.5 mg of fosphenytoin is equivalent to 1 mg of phenytoin.

v) Benzodiazepams are required in up to 15% of neonatal seizure. Commonly used are Diazepam, Lorazepam, and Midazolam. Diazepam (0.25 mg/kg I.V, 0.5 mg/kg rectally) is generally avoided as it has short duration of action, narrow therapeutic window and because of presence of sodium benzoate as preservative. Lorazepam (0.05 mg/kg I.V over 2-5 minutes) has longer duration of action and less adverse effects when compared to diazepam. Midazolam (0.15 mg/kg as I.V bolus) is faster in action than lorazepam and it can be used as infusion(0.02-0.06 mg/kg/hr).

According to Volpe, response to anticonvulsants are 40% after initial 20 mg/kg of phenobarbitone, 70% after 40 mg/kg of phenobarbitone, 85% after 20 mg/kg of phenytoin, 95% to 100% after 0.05mg/kg of lorazepam. Second line drugs are used when seizures are refractory to above line of management. They are lidocaine, paraldehyde, sodium valproate. Lidocaine is usually started with 4 mg/kg/hr I.V on first day and reduced by 1 mg/kg/hr on subsequent day. Paraldehyde 0.1 ml to 0.2 ml/kg i.m or 0.3 ml/kg mixed with coconut oil in 3:1 ratio and given per rectally. Sodium valproate 20-25 mg/kg loading dose followed by 5- 10 mg/kg 12^{th} hourly is used.

Other therapies: Pyridoxine- 50 to 100 mg I.V followed by 10 to 100 mg/day depending upon response have been used.

Exchange transfusion- indicated in life threatening metabolic disorders, accidental injection of local anaesthetic , transplacental transfer of maternal drug (e.g chlorpropamide) and in hyperbilirubinemia to prevent bilirubin encephalopathy.

PROGNOSIS

The most important determinant of outcome is underlying neurological illness. Additionally, seizures of early onset, frequent or prolonged seizures, and seizures that are refractory to multiple anticonvulsant treatment are often associated with poor prognosis. In infants with neonatal seizure after arterial or venous vaso- occlusive disease, seizure is relatively benign. Approximately 75% of infants with cerebral vein thrombosis have favourable outcome. Infants with neonatal seizure secondary to HIE have 50% chance of normal development. Similarly, about 50% of infants with neonatal seizure due to bacterial meningitis have favourable outcome.[8] In term newborns, normal background activity on the EEG is rarely associated with neurological sequelae, whereas severe abnormality of background activity, e.g., burst suppression or marked voltage suppression is associated with abnormal outcome in over 90% of cases. The number of electrographic seizures and the rate of improvement of serial EEG's is also a useful prognostic factor.[32] Neonatal seizures in preterm infants shows high mortality up to 80% in some studies, and a significantly higher risk of adverse neurologic outcome in survivors, when compared to term infants.

The outcome of neonates with neonatal seizures has changed in recent years due to improved prenatal care, better obstetrical care and intensive neonatal care. However, neonatal seizures remain an important predictor of future neurological complications. Various studies have been conducted to identify risk factors for poor neurological outcome.

TEKGUL *et al* conducted a study in Boston between 1997 and 2000, included all newborns admitted to the NICU to describe etiologic profile of neonatal

seizure, the neurodevelopemental outcome, and reliable prognostic indicators of outcome for infants surviving neonatal seizures. Eighty-nine term infants with clinical neonatal seizures underwent neurologic examination, electroencephalography (EEG), neuroimaging, and extensive diagnostic tests in the newborn period. After discharge, all infants underwent regular neurologic evaluations at 12 to 18 months and formal neurodevelopmental testing. Prognostic value of seizure aetiology, neurological examination, EEG and neuroimaging were assessed in this study. Mortality observed in this study was 7%. Seven causes for the seizures were identified in 78 babies , most common etiologies for neonatal seizures were global cerebral hypoxic-ischemia, cerebral vaso-occlusive lesions, and intracranial hemorrhage. Global cerebral hypoxia-ischemia(HI), the most common etiology, was responsible for the large majority of infants with poor long-term outcome. The statistical relationship between neonatal seizure etiology and poor outcome was highly significant. Etiologies associated with poor outcome included cerebral dysgenesis, global cerebral HI, and central nervous system infection. Conversely, infants with focal cerebral HI, transient metabolic disturbances, or idiopathic seizures had an almost universally favorable outcome. Type of seizure was not found to be associated with poor neurodevelopmental outcome. Normal neurological examination during NICU stay, within 28 days of life and in early infancy had favourable outcome at 1 year and 18 months. However abnormal neurological examination during the neonatal period and in early infancy was not a reliable predictor. Moderate to severe background EEG abnormalities were strong predictors of poor neurological outcome. These background EEG pattern has added significant value to the prognostic power over aetiology, only in the global hypoxic-ischemic group

regardless of the timing of the EEG . There was no use of considering the rate of recovery of EEG in predicting the poor neurodevelopmental outcome. Normal neuroimaging and infants with focal cortical infarcts had favourable neurodevelopmental outcome, whereas infants with deep grey matter lesions or multifocal or diffuse cortical lesions invariably had poor neurodevelopmental outcome. Normal neuroimaging and mild abnormal EEG or normal EEG in the neonatal period had favourable neurodevelopmental outcome. The study concludes that seizure aetiology and background EEG pattern remains the powerful prognostic factors.[14]

PISANI *et al* conducted a study in 106 newborns who had neonatal seizures. They were followed up for 24 months and neurological outcome was measured. Six variables were identified as the most important independent risk factors for adverse outcome and were used to construct a scoring system: birth weight, Apgar score at 1 minute, neurologic examination at seizure onset, cerebral ultrasound, efficacy of anticonvulsant therapy, and presence of neonatal status epilepticus. Birth weight less than 2.5 Kg in babies with neonatal seizure had significant adverse neurological outcome. Neuroimaging in neonatal seizure with cranial ultrasound findings of IVH of grade III and IV, intraparenchymal hemorrhage, periventricular leukomalacia, cerebral malformation were strong prognostic indicators of adverse neurological outcome. Neonatal seizures with status epilepticus was associated with poor neurological outcome. Prolonged seizures can be related to specific clinical conditions with a known favourable outcome, like focal clonic seizure in neonatal hypocalcemia; whereas neonatal status epilepticus is almost always of symptomatic origin and is more likely to

be related to diffuse and extensive structural brain injury, which is likely to have a significant influence on outcome. Moderately abnormal neurological examination, no response to anticonvulsant therapy and Apgar score less than 7 at one minute of life were independent risk factors for adverse neurological outcome. EEG with moderate to severe abnormality had poor neurodevelopmental outcome. Based on above six variables two scoring system were proposed one with six variables excluding EEG abnormality, second scoring system including the EEG abnormality. The clinical score was designed to be easily applicable in the first day of the neonatal seizures and accurate in identifying newborns who will have an unfavourable outcome. Type of seizure and onset of seizure did not had significant adverse neurological outcome.[33]

IYPE *et al* conducted a prospective follow-up study of newborns with seizures, to determine the predictors of adverse neurological outcome. 135 babies were recruited; of whom 10 died and 25 were lost to follow up. All enrolled newborns were followed up at 2 and 4 months of age. The outcome was defined as "abnormal" in any of three conditions: (*i*) death either while in the NICU or during follow up (*ii*) post neonatal epilepsy (seizure recurrence) or (*iii*) abnormal neurodevelopment defined as the presence of a motor deficit, developmental delay or spasticity. A few neonates were followed up to 8 months of age. Out of 100 who came for follow up, 32 had developmental delay. Of those with developmental delay 7 of the babies followed up had post neonatal epilepsy, 24 had spasticity, 10 had abnormal vision and 5 had defective hearing at the four month follow-up. 68 babies were normal at follow up. Birth weight, gestational age, head circumference at birth, and age of first seizure could not predict

adverse outcome in this cohort. EEG changes were associated with abnormal development although it could not predict post neonatal epilepsy. The study also found a significant association between patients with an adverse neurological outcome and the interictal EEG. Predominance of spike waves in the EEG can be probably taken as a marker of abnormal neurological outcome. Hypocalcemia was significantly associated with mortality. No risk factors could be identified for post neonatal epilepsy. The study concluded that majority of neonatal seizures had normal outcome with no developmental delay or neurological deficit. Predominantly spike waves in the EEG was predictive of abnormal neurological outcome.[34]

RONEN *et al* conducted a population based prospective study in Canada to examine the outcome and to explore for prognostic markers in a cohort <10 years following neonatal seizures. 90 subjects were involved in the study. Variables associated with poor prognosis were Sarnat stage III or equivalent severe encephalopathy, cerebral dysgenesis, complicated intraventricular hemorrhage, infections in the preterm infants, abnormal neonatal EEGs, and the need for multiple drugs to treat the neonatal seizures. Pure clonic seizures without facial involvement in term infants suggested favorable outcome, whereas generalized myoclonic seizures in preterm infants were associated with mortality. The severity and timing of the pathologic process continues to be the major determinants for outcome.[35]

BRUNQUELL *et al* studied 77 newborns admitted in NICU to determine whether clinical features of neonatal seizures were of value in predicting the neurological outcome. 43% had cerebral palsy at mean follow up of 3.5 years.

Subtle seizure and generalized tonic seizures had higher prevalence of cerebral palsy, mental retardation and epilepsy. In addition subtle seizures were associated with abnormal neurological examination on follow up. Other seizure types did not show significant association with adverse neurological outcome. The study also found that more than two seizure types had significant adverse neurological outcome. The study concludes that clinical semiology is predictive of outcome in neonates with seizures and suggests the presence of unique pathophysiologic processes for different seizure types.[36]

GARFINKLE *et al* conducted a retrospective analysis of 62 term neonates with clinical neonatal seizure to determine potential clinical prognostic factors for term infants with neonatal seizures subsequent to intrapartum asphyxia. A total of 23 (37%) infants had a normal outcome, 34 (55%) survived with 1 or more neurodevelopmental impairments (23 cerebral palsy, 28 global developmental delay, 15 epilepsy, with 18 having combination of two, and 9 having all three), and 5 (8%) died. Six variables were associated with an adverse outcome, but only the presence of meconium aspiration, a low (≤ 3) 1-minute Apgar score, seizure type other than focal clonic, and moderately severely abnormal electroencephalography (EEG) background findings were independently associated with an adverse outcome.[37]

NUNES *et al* conducted a cohort study in a tertiary care hospital. 3659 newborns were admitted and 2.7% were diagnosed to have seizures. 25 died during the neonatal period and another 9 died during first year of life. 35 had developmental delay, 19 had post neonatal epilepsy and 11 had association among this two comorbidities. Most common etiology was hypoxic ischemic

encephalopathy (51%) followed by transient metabolic disturbances (14%), infection (9%)- congenital, septicemia, bacterial meningitis intraventricular hemorrhage (6%), venous infarct (3%), inborn error of metabolism and cerebral dysgenesis (2% each). It was not possible to determine etiology of seizures in 10 patients. No significant statistical relationship between etiology and the outcome studied was observed. Prematurity, low birth weight, abnormal neonatal neuroimaging, abnormal postnatal EEG, postnatal neuroimaging and earlier postnatal seizures were risk factors for developmental delay. The study concluded that neonatal seizures predominated in term newborns and on follow up had increased risk of developmental delay and post neonatal epilepsy. Abnormal post-neonatal EEG and neuroimaging were good predictors for the outcome of developmental delay.[38]

TUDEHOPE *et al* studied 156 newborns with neonatal seizures over 5 years to describe clinical spectrum in neonatal seizure and its outcome. Incidence of neonatal seizure was 3/1000 live births. Predominant risk factors for seizure were prematurity, intrauterine growth retardation, low 5 minute apgar score, preeclampsia, antepartum hemorrhage, twin pregnancy and breech presentation. The predominant seizure type was tonic in 28.6%, multifocal clonic in 27.2%, subtle in 18.4%, myoclonic in 15.0% and focal clonic in 8.8%. Mortality (31%) and long-term disability (43%) rates were high. Tonic seizures had the highest mortality and morbidity. Causative factors were determined in 95% of convulsing infants, most frequent being hypoxic-ischaemic encephalopathy (40.3%) and cerebroventricular haemorrhage (30.5%). A poor long-term prognosis was associated with prolonged convulsions, tonic and multifocal clonic convulsions,

convulsions due to asphyxia and cerebroventricular haemorrhage and an abnormal neurological examination at discharge.[39]

ARTHUR *et al* report on their experience gained through a prospective study of 144 infants who developed seizures during the first 3 weeks of life. Only full-term neonates weighing 2.5 kg or more were included. Follow up averaged four years. Seven subjects were lost on follow up leaving a total of 137. The study showed high mortality and morbidity for neonates with seizure states, the outcome being poor for half of the cases. The study found out that prognosis based on abnormal or normal neurological signs in a convulsing neonate showed poor correlation with the state of the child when re-evaluated years later. Neonates with seizure and normal EEG had 86% chance of normal neurodevelopmental outcome, regardless of other clinical data's. In contrast neonates with either a flat, periodic, or multifocal EEG had only 7% chance of normal development.[40]

KIM *et al* studied 41 newborn with neonatal seizure over three years and evaluated with special references to risk factors, neurological examination, laboratory data, neuroimaging, EEG abnormalities, type of seizure, response to treatment and prognosis. EEG done for 32 cases, 17 out of 32 cases showed abnormal EEG record. Multifocal seizure was predominant seizure type followed by subtle seizure., 30% of subtle seizure had adverse neurological outcome, 24% of multifocal seizure had adverse neurological outcome, while myoclonic seizure had favourable outcome. Overall prognosis was relatively good except for those with abnormal EEG background . The study concluded that neonatal seizure may permanently disrupt the brain development, hence better understanding of the

neonatal seizure's clinical profile and their management may lead to reduction of neurological disability in their later childhood.[6]

ALMUBARAK *et al* conducted a retrospective study of 118 term newborns who had EEG taken in the first month of life. They were followed at 4 years and 16 years of age and assessed for neurological outcome. Clinical neurologic outcome was classified into favourable when patients had no or only mild limitation in assessment, unfavourable when patients had moderate to severe abnormalities in assessment. Of the 118 neonates, 36 (30.5%) had favourable and 82 (69.5%) had unfavourable outcome. Sixty-seven (57%) had abnormal EEG background of which 56 had both unfavourable outcome and epilepsy; 102 (86%) had sharp transient discharges of which 75 had unfavourable outcome; 20 (17%) had ictal epileptiform discharges of which 18 had unfavourable outcome; 98 (83%) had abnormal overall EEG record, of which 77 had unfavourable outcome.[41]

MELLITS *et al* conducted a prospective study of 54,000 pregnant women enrolled in National collaborative perinatal project (NCPP), infants of these women who had neonatal seizure were followed up for 7 years to analyze association of perinatal events with adverse outcome and to analyze factors predictive of outcome. 5 minute apgar score less than 7, need of resuscitation after 5 minutes of life, time of onset of seizure and seizure lasting for more than 30 minutes were best early predictors of significant neurological sequelae.[42]

SINGH M *et al* studied 107 babies with neonatal hypoglycemia over 15 months period to analyze the neurodevelopmental outcome among the asymptomatic hypoglycemia and symptomatic hypoglycemia. Asymptomatic

hypoglycemia was found in 64 newborns and 43 were symptomatic hypoglycemia. Asymptomatic hypoglycemia occurred earlier than symptomatic hypoglycemia. Symptomatic hypoglycemia had lower blood glucose than asymptomatic hypoglycemia. On neurodevelopment follow up the mental developmental index (MDI) and the psychomotor developmental index (PDI) of symptomatic babies with seizures were significantly lower as compared to those with other features of hypoglycaemia as well as asymptomatic babies. The duration of hypoglycaemia was directly related to the MDI. This study indicates that there is a need to identify babies vulnerable to symptomatic hypoglycaemia more precisely.[43]

A .L. GORDEN *et al* conducted a retrospective study in Kenya to assess the neurological and developmental outcome of neonatal sepsis and neonatal jaundice in rural Kenya. The study recruited 87 cases, 23 were neonatal jaundice, 24 were neonatal sepsis, and 40 were controls. Subjects were assessed at 18 to 32 months of age. The case with neonatal sepsis had significantly more motor and eye-hand difficulties than the controls.[44]

Nair MKC *et al* developed Trivandrum Development Screening Chart (TDSC), a simple screening tool to assess developmental delay at the community level. TDSC was designed by selecting 17 items from Bayley Scales of Infant Development (Baroda norms). It was validated both at hospital and community level against standard Denver Development Screening Test. TDSC has sensitivity of 66.7% and specificity of 78.8% which makes it an acceptable simple screening tool even for community level workers.[45]

OBJECTIVES

STUDY OBJECTIVES

To assess the neurodevelopemental sequelae of neonatal seizure of newborns admitted in NICU at Govt. Stanley medical college hospital.

To identify the risk factors for poor neurodevelopemental outcome in neonatal seizures.

SUBJECTS & METHODS

SUBJECTS AND METHOD

STUDY PLACE

This study was conducted at neonatal intensive care unit of Institute Of Social Paediatrics and Govt.RSRM hospital, a tertiary care hospital, Royapuram, Chennai.

STUDY PERIOD: march 2010 to august 2011

STUDY DESIGN: prospective study

STUDY POPULATION: Newborns admitted in neonatal intensive care unit of Institute Of Social Paediatrics and Govt. RSRM hospital during first six months of the study period were included in the study.

INCLUSION CRITERIA: Following newborns were included in the study.

-Term babies weighing > 2.5 Kg.

- Seizures occurring < 28 days of life.

EXCLUSION CRITERIA: Following newborns were excluded from the study.

- Preterm babies < 37 weeks

- Babies with congenital malformation of brain.

-birth weight <2.5kg

SAMPLE SIZE : All newborns who satisfied the above mentioned inclusion criteria were recruited during the first six months of the study.

STUDY METHODOLOGY

All term newborns with neonatal seizures admitted in NICU satisfying the inclusion criteria during March 2010 to august 2011 were enrolled in the study. Informed consent was obtained from the parents and ethical committee approval was obtained for the study. A detailed antenatal history from the mother was obtained. Birth history regarding mode of delivery, place of delivery, Apgar score, birth weight were obtained. A detailed clinical examination of the baby was done; anthropometry measuring head circumference, length, weight, chest circumference was recorded . Relevant laboratorial investigations measuring plasma glucose, serum calcium, complete blood count, serum C-Reactive protein, blood culture and sensitivity , lumbar puncture to analyze CSF, serum electrolytes, USG cranium, EEG and CT brain were done . Results were documented in the proforma . Babies were treated as per the standard protocol. Each baby was followed in NICU daily till their discharge and given a child guidance clinic number (CGC). After discharge babies were followed up in well baby clinic and department of paediatric neurology at 1 , 3, 6, 9 and 12 months. At each visit babies were screened for developmental delay using Trivandrum Developmental Screening Chart, detailed clinical examination assessing tone, reflex, posture and paucity of movements. Trivandrum development screening chart consist of 17 items to assess developmental progression up to 2 years of age. Each item is represented as a horizontal bar, left end of the bar represents 3% and right end represents 97% of the population who should have achieved the milestone. Each milestone is represented by a bar. Infant is considered to have development delay if it has not achieved the particular milestone at the

upper limit of the bar physiotherapy. Anthropometry measurement of head circumference (microcephaly and macrocephaly), weight gain, length were assessed with WHO growth charts. . Babies with abnormal neurodevelopemental delay were treated with multidisciplinary care; and at the end of one year various data were collected and statistical analysis was done with SPSS software.

STASTISTICAL ANALYSIS

Statistical analysis of neuro developemental outcome was done using Pearson –Chi Square test with SPSS software.

RESULTS AND ANALYSIS

In our study conducted at Institute Of Social Paediatrics, newborns with neonatal seizure enrolled from March 2010 to August 2011 were followed till one year of age. Total number of cases were 108 babies with neonatal seizure , of which 8 parents were not willing to get enrolled in the study. Of the remaining 100 cases enrolled, 4 babies died during the hospital stay (4%), 96 babies were given CGC number and followed, 5 babies were lost in follow up. At the end of one year 91 infants completed the study. At the end of the study, the data was evaluated using Microsoft Excel Spreadsheet and the neurodevelopment outcomes were measured using Pearson Chi-square test.

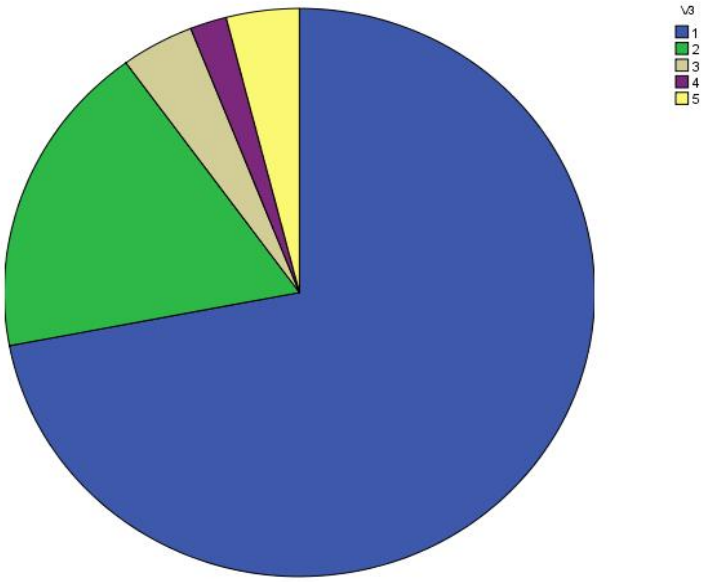
TABLE I

Sex of the baby	**No of cases**	
	N=100	**%**
Male	52	52
Female	48	48

Out of 100 babies enrolled in our study, 52 were male babies (52%) and 48 were female babies (48%). Among the 100 newborns 4 newborns died (4%)- 3 male babies and one female baby. Of the remaining 96 newborns , 5 were lost in follow up (5%)- 3 male babies and 2 female babies.

PLACE OF DELIVERY

FIGURE I



1) Govt RSRM hospital 2) Corporation hospital 3) PHC 4) HSC 5) private hospital

In our study 72 babies were delivered at Govt. RSRM hospital (72%), 18 babies were delivered in corporation hospital and referred to our hospital for neonatal seizure (18%), 4 newborns were delivered and referred from PHC and private hospitals each, for neonatal seizure (4%) , and 2 (2%) newborns were delivered in HSC and referred to our institution for neonatal seizure.

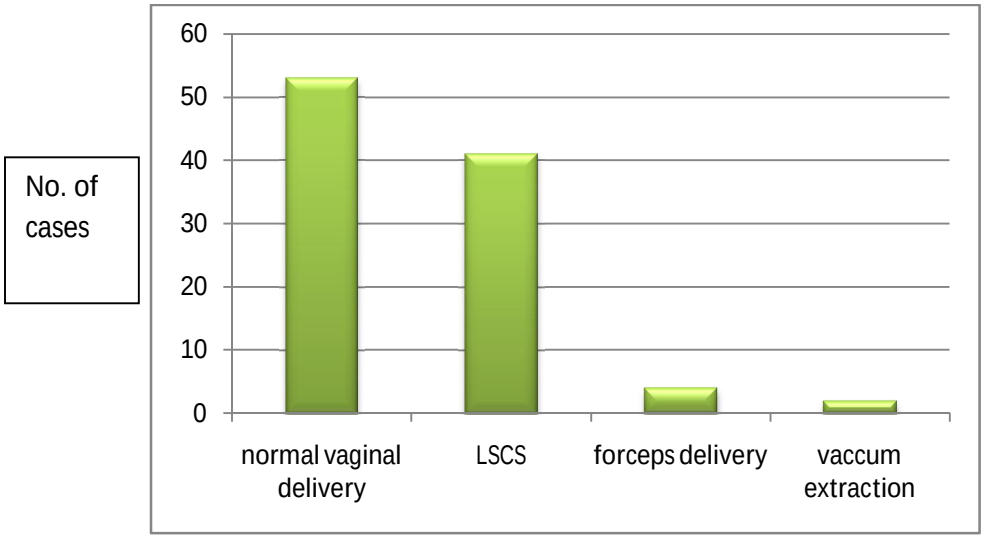
TABLE II

Sex of the baby	No of cases	
	N=91	%
Male	46	50.5
Female	45	49.5

At the end of study 46 male babies and 45 female were left for assessment of neurodevelopemental sequelae.

MODE OF DELIVERY

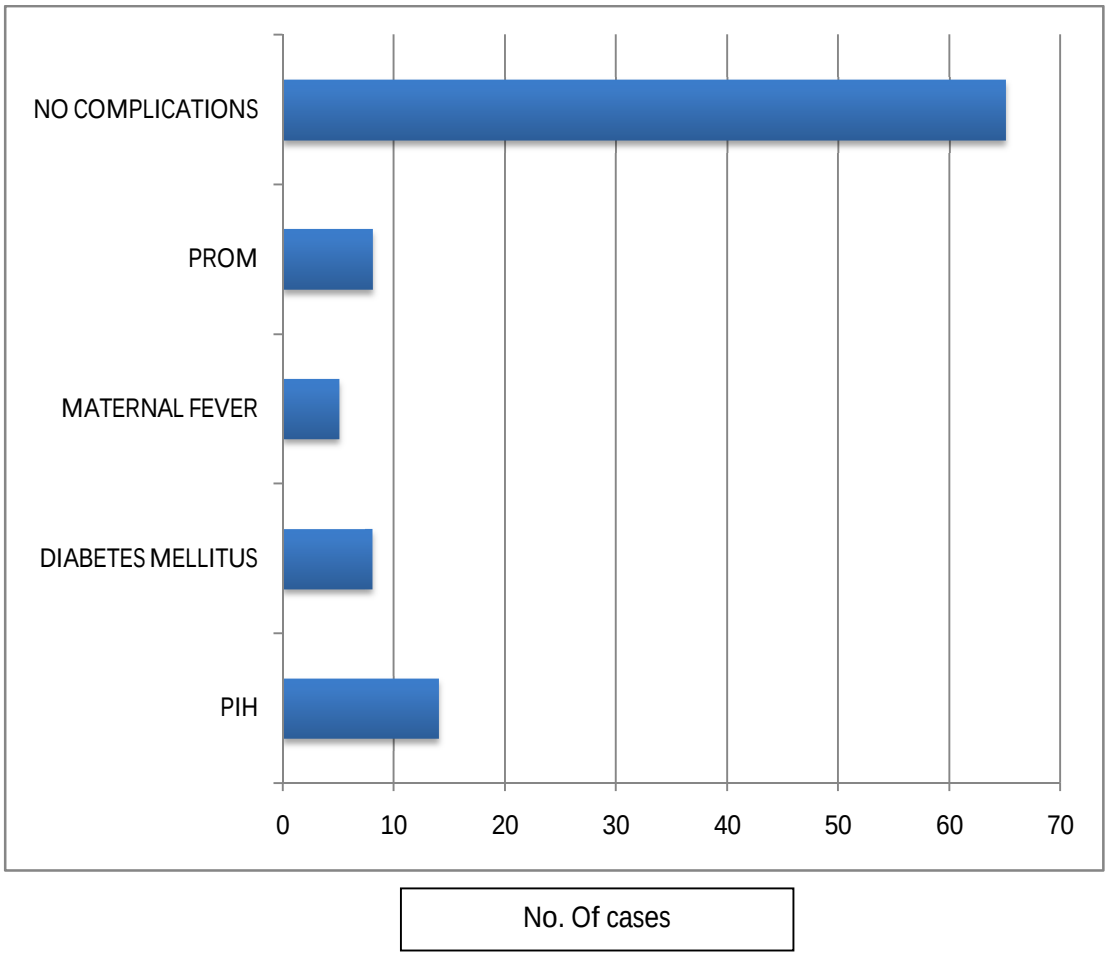
FIGURE II



In our study 53 newborns were delivered by normal vaginal delivery (53%) , 41 newborns were delivered by LSCS (41%), 4 newborns were delivered by forceps delivery(4%). 2 newborns were delivered by vacuum extraction(2%). Among the 2 babies born by vaccum extraction both the babies expired during the hospital stay. Among 4 cases born by forceps delivery one was lost in follow up, another one expired during the hospital stay.

ANTENATAL COMPLICATIONS

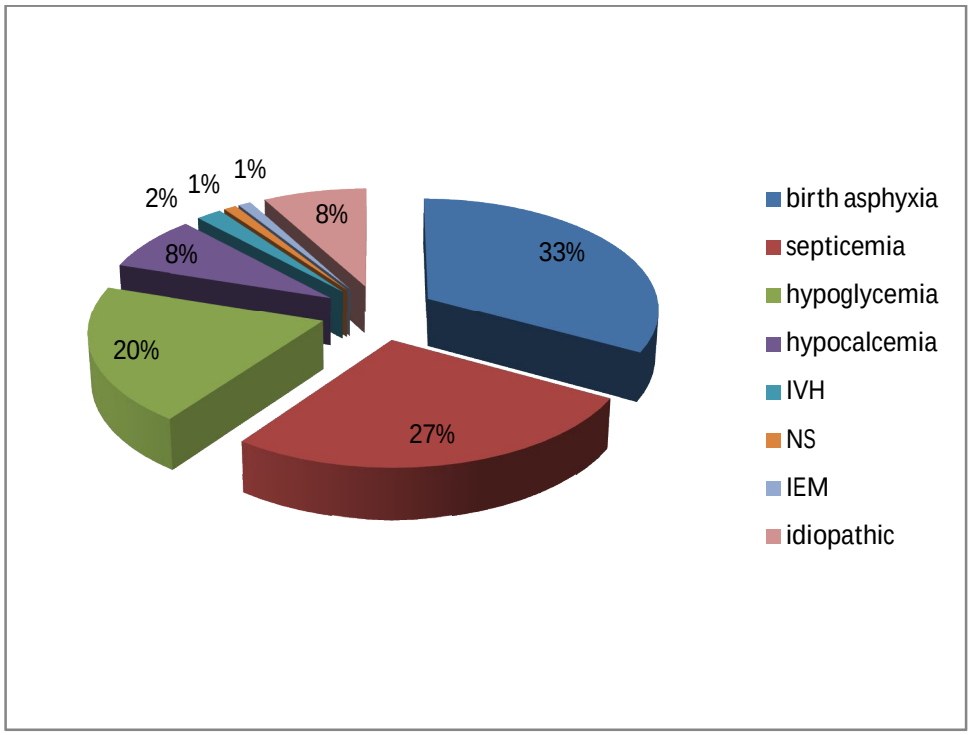
FIGURE III



In our study 14 mothers (14%) had pregnancy induced hypertension, 8 mothers (8%) had diabetes mellitus of which 1 mother had insulin dependent diabetes mellitus and rest of them gestational diabetes mellitus.5 mothers had maternal fever(5%), 8 mothers had premature rupture of membranes (8%) and 65 mothers didn't had any antenatal complications.

ETIOLOGICAL PROFILE OF NEONATAL SEIZURE

FIGURE IV



Among the 100 cases 33 (33%) had birth asphyxia , 27 newborns (27%) had septicaemia, 20 newborns had hypoglycaemia(20%), 8 newborns had hypocalcemia, 2 newborns had intraventricular haemorrhage (both were grade II haemorrhage), diagnosed with ultrasound cranium. one newborn was diagnosed to have neonatal stroke who presented with paucity of movements of left upper limb and the left lower limb; CT brain showed hypo dense infarct area in the right hemisphere, CT angiogram could not be done as facility was not available in our hospital. one newborn had seizure due to inborn error of metabolism(1%). Eight newborns had seizures for which cause could not be identified(8%).

ONSET OF SEIZURE

FIGURE V

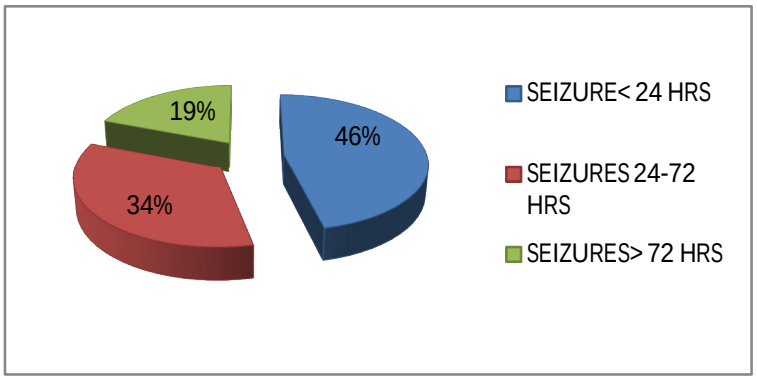


TABLE III

ONSET OF SEIZURE	NO OF CASES	
	NO OF CASES (N=100)	%
< 24 HRS	46	46
24 TO 72 HRS	34	34
> 72 HRS	20	20
4-7 days	8	
8-14 days	7	
>14 days	5	

In our study 46 newborns developed seizures less than 24 hours(46%), 34 developed seizures between 24 to 72 hrs, 20 cases developed seizures after 72 hours of life. In our study most of the seizures occurred within 24 hours of life.

CORRELATION BETWEEN ONSET OF SEIZURE AND ETIOLOGY

TABLE IV

ETIOLOGY (n=100)	ONSET OF SEIZURE		
	< 24 hrs (n=46)	24 – 72 hrs (n=34)	>72 hrs (n=20)
Birth asphyxia(33)	18	15	-
Septicemia(27)	3	12	12
Hypoglycemia(20)	12	4	4
Hypocalcemia(8)	4	2	2
IVH(2)	1	-	1
NS(1)	1	-	-
IEM(1)	1	-	-
Idiopathic(8)	6	1	1

In our study birth asphyxia was the most common cause of neonatal seizure accounting 33% of the total cases of neonatal seizure. Among the 33 cases 18 cases developed seizure within 24 hrs(54%), 15 developed seizure between 24 hrs to 72 hrs(45%). Among the 27 cases of septicaemia 3 babies developed seizure within 24 hrs(20%), 12 developed seizure between 24 hrs to 72 hrs(80%), and another 12 developed seizure after 3rd day. While most of the hypoglycaemic seizures occurred less than 24 hrs of life(60%). 50% of the hypocalcemic seizures occurred in less than 24 hrs of life, while 25% of seizures occurred between 24 hrs to 72 hrs and remaining 25% of the seizures occurred after 72 hrs. Among the intraventricular haemorrhage one developed seizure within 24 hrs of life, another developed seizure after 72 hrs. Six of the seizures for which cause could not be identified, developed seizure within 24 hrs. Neonatal stroke and inborn error of metabolism developed seizure within 24 hrs.

TYPE OF SEIZURE

FIGURE VI

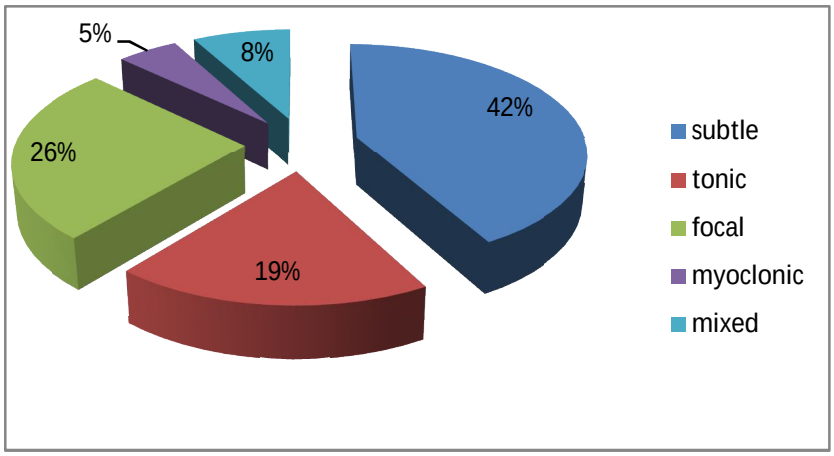


TABLE V

TYPE OF SEIZURE	NO OF CASES	
	N=100	%
Subtle	42	42
Tonic	19	19
Focal	26	26
Myoclonic	5	5
Mixed	8	8

In our study seizures were observed clinically, and following five types were documented . 42% of seizures were subtle seizures, focal seizures were 26 cases, tonic seizures were 19(19%). Eight newborns had mixed seizures(8%). Myoclonic seizures was observed in 5 newborns(5%).

CORRELATION BETWEEN TYPE OF SEIZURE AND ETIOLOGY

TABLE VI

Etiology(n)	Type of seizure(n)				
	Subtle (42)	**Tonic (19)**	**Focal (26)**	**Myoclonic(5)**	**Mixed (8)**
Birth asphyxia(33)	17	5	6	2	3
Septicaemia(27)	10	5	9	1	2
Hypoglycaemia(20)	9	4	5	0	2
Hypocalcemia(8)	1	5	2	0	0
IVH(2)	0	0	1	1	0
NS(1)	0	0	1	0	0
IEM(1)	1	0	0	0	0
Idiopathic(8)	4	0	2	1	1

Birth asphyxia accounted for majority of cases of neonatal seizure, among them 17 cases were subtle seizures (51%), 5 cases were tonic seizures(15%), 6 cases were focal seizures(18%). Out of 27 cases septicemia, most common seizure was subtle seizure(37%), followed by focal seizure(30%). Out of 20 cases of hypoglycemia, 9 cases were subtle seizure(45%), 5 were focal seizure(25%), 4 were tonic seizures (20%).

CORRELATION BETWEEN TYPE OF SEIZURE AND ONSET OF SEIZURE

TABLE VII

Type of seizure (n)	**Onset of seizure no of cases(n)**		
	<24 hrs (46)	**24 – 72 hrs(34)**	**>72 hrs (20)**
Subtle (42)	25	13	4
Tonic (19)	10	3	6
Focal (26)	9	13	4
Myoclonic (5)	1	2	2
Mixed (8)	1	3	4

Of the 46 cases of seizures occurring less than 24 hrs, 25 cases were subtle seizures. Out of this 25 subtle seizures 13 cases occurred during 24 to 72 hrs and 4 cases occurred after 72 hrs. Out of 26 focal seizures 13 cases occurred between 24 to 72 hrs, 9 cases occurred within 24 hrs. All the 5 myoclonic seizures occurred after 24 hrs. Tonic seizures mostly occurred within 24 hrs (52%). More than 50% of mixed type of seizures occurred after 24hrs

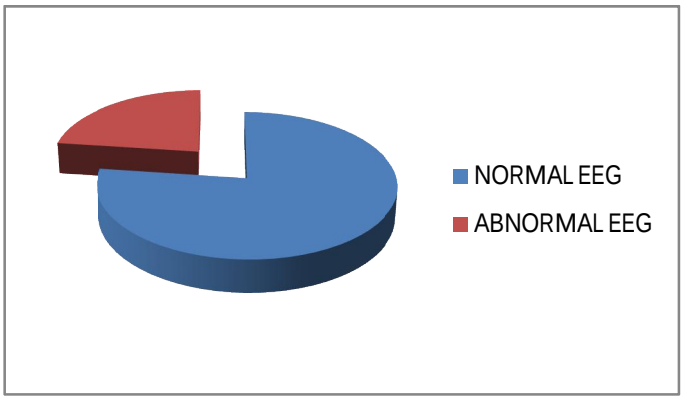
ABNORMAL EEG RECORD

TABLE VIII

EEG	NO OF CASES
NORMAL	74
ABNORMAL	22

EEG was taken for 96 cases among which 74 records were normal, 22 cases showed abnormal record mostly in the form of abnormal background activity. EEG was not taken for 4 cases as they died during the hospital stay.

FIGURE VII



PROPORTION OF NORMAL AND ABNORMAL EEG RECORD

CORRELATION BETWEEN ABNORMAL EEG AND ETIOLOGY OF SEIZURE

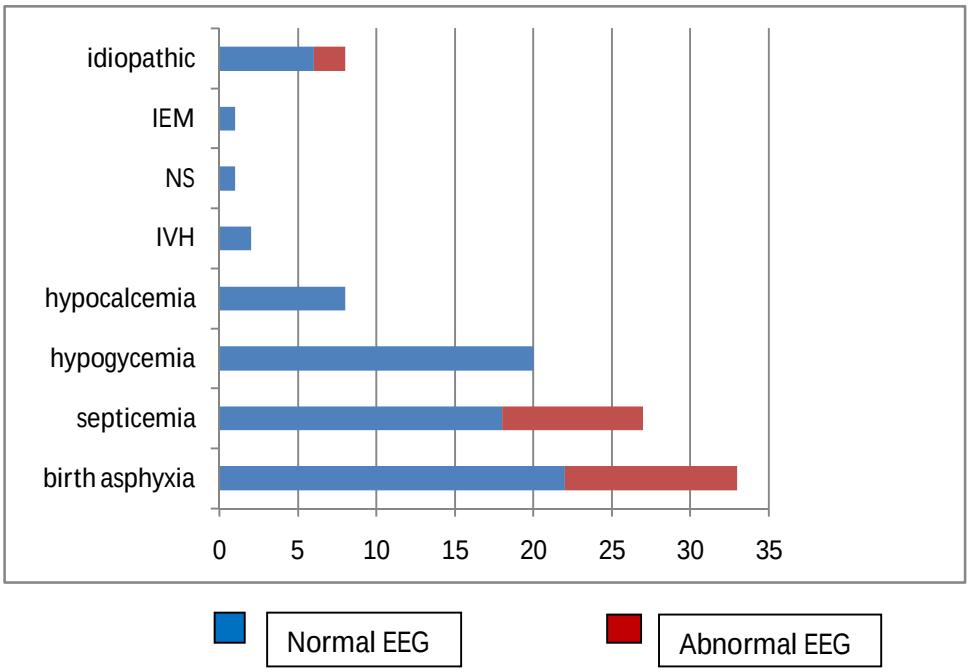
TABLE IX

Etiology (n)	EEG (no of cases)	
	Normal	**abnormal**
Birth asphyxia(33)	22	11
Septicaemia(27)	18	9
Hypoglycemia(20)	20	0
Hypocalcemia(8)	8	0
IVH(2)	2	0
NS(1)	1	0
IEM(1)	1	0
Idiopathic(8)	6	2

Among 33 cases of birth asphyxia 11 cases had abnormal EEG record(33%), while 50% of septicaemia cases had abnormal EEG record,(i.e. 9 cases among 18 cases of neonatal sepsis). Among the 8 cases for which cause could not be identified, 2 cases had abnormal EEG record(33%). Hypoglycemia and hypocalcemia did not show abnormal EEG record.

ETIOLOGY VS ABNORMAL EEG

FIGURE VIII



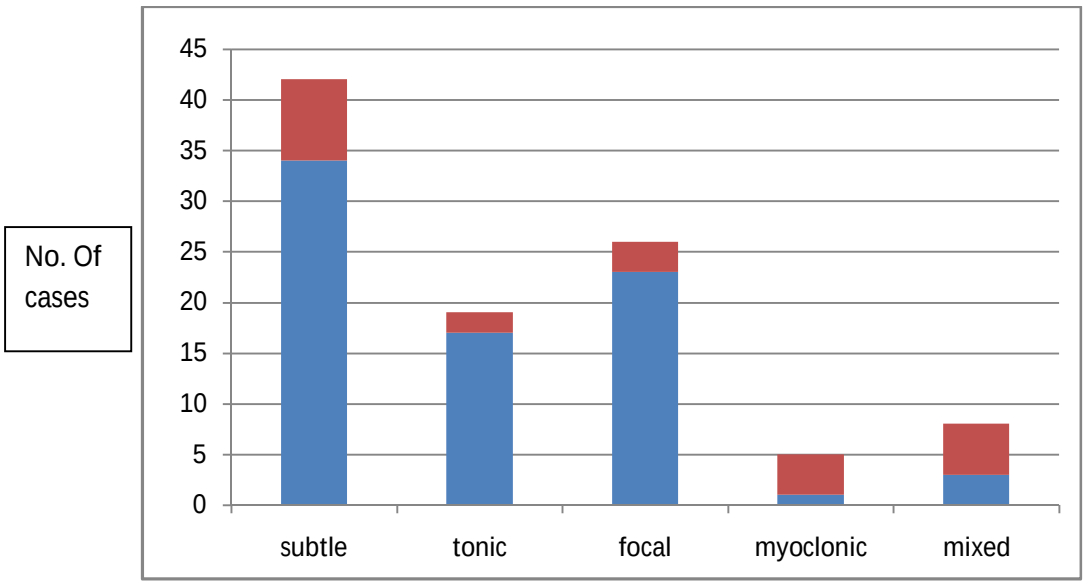
CORRELATION BETWEEN EEG AND TYPE OF SEIZURE

TABLE X

Type of seizure	EEG (No of cases)	
	normal	abnormal
Subtle(42)	34	8
Tonic(19)	17	2
Focal(26)	23	3
Myoclonic(5)	1	4
Mixed(8)	3	5

Among the 22 cases of abnormal EEG record majority of cases were due to subtle seizures(36%). Out of 5 cases of myoclonic seizures 4 cases had abnormal EEG record(80%). 62.5% of cases of mixed type of seizure had abnormal EEG record. While 19.04% of subtle seizures, 10.5% of tonic seizures, 11.5% of focal seizures had abnormal EEG record.

FIGURE XI



TYPE OF SEIZURE VS ABNORMAL EEG RECORD

RESULTS AND ANALYSIS

Various parameters were assessed for developmental delay, microcephaly and macrocephaly. Among the 100 cases enrolled, 4 cases died during the hospital stay, 5 cases were lost in the follow up. Of the remaining 91 cases developmental assessment was done, 22 cases had only developmental delay (24%), 10 cases had isolated microcephaly(10.9%), 3 cases had combination of microcephaly with developmental delay (3.2%) and 2 cases had combination of macrocephaly with developmental delay. Statistical analysis was done for 91 cases who had completed the study using SPSS 16 software.

TABLE XI

SEX(n)	**Developmental delay (n)**		**p value**
	absent (69)	**present (22)**	
MALE(46)	35	11	0.953
FEMALE(45)	34	11	

In our study, out of 46 male babies 11 had developmental delay(23%), among the 45 female babies , 11 had developmental delay(24%). No statistically significant difference was observed among sexes in the occurrence of developmental delay.(p value=0.953)

RESULTS & ANALYSIS

TABLE XII

SEX(n)	Isolated microcephaly(n)		Both microcephaly& developmental delay (n)		Both macrocephaly& developmental delay (n)	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
MALE(46)	6	40	1	45	2	44
FEMALE(45)	4	41	2	43	0	45
p value	0.52		0.544		0.157	

In our study, 13% of male babies had isolated microcephaly and 8% of female babies had isolated microcephaly. There was no statistically significant difference among sexes in the occurrence of isolated microcephaly (p value=0.52).

There was no significant difference among sexes in the occurrence of 'microcephaly with developmental delay' (p value=0.544). Occurrence of 'macrocephaly with developmental delay' (2.1%) did not show any statistically significant difference among the sexes.

TABLE XIII

MODE OF DELIVERY(n)	Developmental delay(n)		p value
	absent(69)	present(22)	
Normal vaginal delivery(50)	40	10	0.36
LSCS(39)	27	12	
Forceps delivery(2)	2	0	

Total-91 cases

In our study 55 cases were delivered by normal vaginal delivery. 2 cases were lost in follow up, one had intraventricular haemorrhage, another had inborn error of metabolism. One died during the hospital stay due to severe sepsis. Remaining 50 cases were followed up and analyzed. Among the 41 cases born by LSCS 2 were lost in the follow up, one had seizure due to birth asphyxia and another had seizure due to septicaemia. So remaining 39 cases were followed up. Of the 2 cases born by vacuum extraction, one died due to intraventricular haemorrhage and another died due to neonatal stroke. On analyzing the outcome of the remaining 91 cases there was no statistically significant difference observed in the occurrence of developmental delay(p value=0.36)

TABLE XIV

MODE OF DELIVERY(n)	Isolated microcephaly(n)		Both microcephaly& developmental delay(n)		Both macrocephaly & developmental delay(n)	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
Normal vaginal delivery(50)	6	44	2	48	1	49
LSCS(39)	4	35	1	38	1	38
Forceps delivery(2)	0	2	0	2	0	2
P value	0.852		0.9		0.96	

Out of 50 cases delivered by normal vaginal delivery, 6 cases had microcephaly; 2 cases had 'microcephaly with developmental delay' and 'macrocephaly with developmental delay' was noted in one case. There was no statistically significant difference in the occurrence of isolated microcephaly(p value=0.852), 'microcephaly with developmental delay'(p value=0.9) and 'macrocephaly with developmental delay'(p value=0.96) and mode of delivery.

TABLE XV

Type of seizure (n)	Developmental delay(n)		p value
	absent(69)	present(22)	
Subtle (38)	27	11	0.53
Tonic (19)	16	3	
Focal (22)	18	4	
Myoclonic(4)	2	2	
Mixed(8)	6	2	

In our study, out of 22 cases of developmental delay 11 cases were due to subtle seizures(50%). On analysis, type of seizure did not have statistically significant difference in the occurrence of only developmental delay(p value=0.53).

TABLE XVI

Type of seizure (n)	Isolated microcephaly(n)		Both microcephaly & developmental delay(n)		Both macrocephaly& developmental delay (n)	
	PRESENT (10)	**ABSENT (81)**	**PRESENT (3)**	**ABSENT (88)**	**PRESENT (2)**	**ABSENT (89)**
subtle (38)	5	33	0	38	0	38
tonic(19)	2	17	1	18	0	19
focal(22)	1	21	0	22	2	20
Myoclonic(4)	0	4	2	2	0	4
Mixed(8)	2	6	0	8	0	8
p value	0.522		0.00009		0.170	

Type of seizure did not have statistically significant difference in the occurrence of isolated microcephaly (p value=0.522). However out of 3 cases of 'microcephaly with developmental delay', 2 were due to myoclonic seizure and one was due to focal seizure. There was significant difference observed with the type of seizure in the occurrence of 'microcephaly with developmental delay' (p value <.05). Out of 91 cases 2 cases had 'macrocephaly with developmental delay', focal seizure was found in both the cases. Type of seizure did not had statistically significant difference in the occurrence of 'macrocephaly with developmental delay'(p value=0.170).

TABLE XVII

Onset of seizure(n)	Developmental delay(n)		p value
	absent(69)	absent(22)	
< 24 hrs(42)	26	16(72%)	0.015*
24-72 hrs(30)	27	3	
>72 hrs(19)	16	3	

In our study it was found, there is a relation between onset of seizure and developmental delay. Out of 91 cases 42 cases developed seizures within 24 hours. Out of this 42 cases 72% of cases had developmental delay which was statistically significant (p value=0.015).

TABLE XVIII

Onset of seizure(n)	Isolated microcephaly(n)		Both microcephaly& developmental delay(n)		Both macrocephaly& developmental delay(n)	
	Present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
<24 hrs (42)	5	37	0	42	0	42
24-72 hrs(30)	3	27	1	29	1	29
>72 hrs (19)	2	17	2	17	1	18
p value	0.966		0.103		0.376	

Out of 91 cases 10 cases developed isolated microcephaly; out of this 10 cases 5 cases(50%) of microcephaly was observed in seizures occurring less than 24 hours, but it was not statistically significant(p value=0.966). Overall there was no correlation between onset of seizures and microcephaly. Out of 91 cases 2 cases developed 'macrocephaly with developmental delay' and 3 cases developed 'microcephaly with developmental delay'. There was no correlation between onset of seizure and the above two parameters.

TABLE XIX

Etiology of seizure (n)	Developmental delay(n)		p value
	absent(69)	present(22)	
Birth asphyxia(30)	21	9	0.671
Septicemia (25)	20	5	
Hypoglycemia(20)	16	4	
Hypocalcemia(8)	7	1	
Idiopathic(8)	5	3	

Out of the 22 cases of developmental delay 40% of cases were due to birth asphyxia. Statistically it was not significant (p value=0.671). Hence there was no correlation between aetiology of seizure and developmental delay in our study.

TABLE XX

Etiology of seizure(n)	Isolated microcephaly(n)		Both microcephaly & developmental delay(n)		Both macrocephaly & developmental delay(n)	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
Birthasphyxia(30	4	26	1	29	0	30
Septicaemia(25)	2	23	1	24	2	23
Hypoglycemia(20	1	19	0	20	0	20
Hypocalcemia(8)	2	6	1	7	0	8
Idiopathic (8)	1	7	0	8	0	8
p value	0.671		0.538		0.249	

In our study there was no correlation between etiology of seizure and isolated microcephaly (p value=0.671), 'microcephaly with developmental delay' and 'macrocephaly with developmental delay'.

TABLE XXI

Hypoglycemia(n)	Developmental delay(n)		p value
	present(69)	absent(22)	
<20 mg (6)	4	2	0.78
21-35 mg (7)	6	1	
36-45 mg(7)	6	1	
>45 mg(71)	53	18	

Out of 91 cases 20 cases had hypoglycemia, out of 20 cases of hypoglycemia had developmental delay and it was not statistically significant.(p value=0.78)

TABLE XXII

Hypoglycemia (n)	Isolated microcephaly(n)		Both microcephaly & developmental delay(n)		Both macrocephaly & developmental delay(n)	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
<20 mg (6)	0	6	0	6	0	6
21- 35 mg(7)	1	6	0	7	0	7
36-45mg (7)	0	7	0	7	0	7
>45 mg(71)	9	62	3	68	2	69
p value	0.59		0.832		0.902	

Out of 20 cases of hypoglycemia, one case had isolated microcephaly, there was no cases of 'microcephaly with developmental delay' or 'macrocephaly with developmental delay'.

TABLE XXIII

EEG(n)	Developmental delay(n)		p value
	absent(69)	present(22)	
NORMAL (69)	60	9	<0.001*
ABNORMAL(22)	9	13	

EEG was taken for 91 cases before discharge and 22 cases showed abnormal background activity. 7 cases had mild abnormal activity while 15 cases had moderate to severe abnormal background activity. Among the 22 cases with abnormal EEG record 13 had developmental delay, 12 with moderate to severe abnormal background activity and one with mild abnormal background activity. There was statistically significant association with developmental delay(p value<0.001)

TABLE XXIV

EEG(n)	Isolated microcephaly(n)		Both microcephaly& developmental delay(n)		Both macrocephaly& developmental delay(n)	
	PRESENT (10)	**ABSENT (81)**	**PRESENT (3)**	**ABSENT (88)**	**PRESENT (2)**	**ABSENT (89)**
Normal (69)	8	61	1	68	1	68
Abnormal (22)	2	20	2	20	1	21
p value	0.741		0.08		0.388	

Among 22 cases with abnormal EEG record on follow up to 1year, 2 cases had isolated microcephaly (p value=0.741); 2 cases had 'microcephaly with developmental delay'(p value=0.08) and 2 cases had 'macrocephaly with developmental delay' (p value=0.38). On statistical analysis no significant difference was observed.

Out of 22 cases with abnormal EEG record, on follow up for 1year, 18 cases had adverse neurodevelopmental sequelae; but 4 cases had normal outcome.

TABLE XXV

AN complication (n)	Developmental delay(n)		p value
	absent(69)	present(22)	
PIH(13)	10	3	0.998
DM(8)	6	2	
Maternal fever(5)	4	1	
PROM(7)	5	2	
Nocomplication(58)	44	14	

Total-91

In our study, 3 newborns delivered to PIH mother who had neonatal seizure had developmental delay, 2 among the 8 born to mother with diabetes mellitus had developmental delay. 20% of newborn with seizure whose mother had fever during perinatal period had developmental delay. 28% of newborn with seizure whose mother had premature rupture of membrane for > 12 hours had developmental delay. On analyzing there was no statistically significant association between antenatal complication and developmental delay(0.998).

TABLE XXVI

AN complication (n)	Isolated Microcephaly (n)		Both microcephaly & developmental delay (n)		Both macrocephaly &developmental delay (n)	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
PIH (13)	2	11	0	13	0	13
DM (8)	0	8	0	8	0	8
Maternal fever(5)	0	5	0	5	1	4
PROM (7)	2	5	0	7	0	7
No complication(58)	6	52	3	55	1	57
p value	0.393		0.779		0.08	

15 % of newborn with neonatal seizure whose mother had PIH had isolated microcephaly and 28% of newborn whose mother had premature rupture of membrane had isolated microcephaly. 10% of newborn whose mother had no antenatal complication had isolated microcephaly. There was no statistically significant difference observed among isolated microcephaly and antenatal complication (p value=0.393).

similarly there was no statistical significance between antenatal complication and 'microcephaly with developmental delay' and 'macrocephaly with developmental delay'.

TABLE XXVII

Apgar at 5min(n)	Developmental delay(n)		p value
	absent(69)	present(22)	
< 3(10)	2	8	<0.001*
3-8(17)	16	1	
>8 hrs(64)	51	13	

Low 5 minute Apgar score was observed in 17 newborns, among them 9 had developmental delay. Among the 9 newborns 8 babies had Apgar score less than 5 at 5 minutes of life. Extended apgar score was not available. On analysis there was statistically significant association between low 5 minute Apgar score and developmental delay (p value< 0.001)

TABLE XXVIII

Apgar at 5 min (n)	Isolated microcephaly(n)		Both microcephaly& developmental delay(n)		Both macrocephaly& developmental delay	
	present (10)	absent (81)	present (3)	absent (88)	present (2)	absent (89)
<3 (10)	1	9	1	9	0	10
3-8 (17)	3	14	0	17	0	17
>8 (64)	6	58	2	62	2	62
p value	0.62		0.3		0.650	

Low 5 minute apgar score was noted in 27 cases. 4 out of 27 cases with low 5 minute Apgar score had isolated microcephaly (p value= 0.62), one out 27 newborns with low 5 minute Apgar score had 'microcephaly with developmental delay' (p value= 0.3). Hence there was significant statistical association was observed between low 5 minute apgar score and 'microcephaly with developmental delay'.

DISCUSSION

DISCUSSION

The current study was undertaken between march 2010 and august 2011. In this study conducted at institute of social paediatrics, and Govt. RSRM NICU we studied the neurodevelopmental outcome of the babies who had neonatal seizure and analyzed the risk factors for the poor developmental outcome. A total of 1856 babies got admitted in NICU, among them 108 term newborns had neonatal seizure. 4 newborns with neonatal seizure expired during the hospital stay.

Sample size in various studies

Study	**sample size**
Iype et al	135
Tekgul et al	89
Kim et al	41
Brunquell et al	77
Arthur et al	144

Out of 108 newborns 91 completed the study, among the 91 infants 22 had developmental delay, 10 had microcephaly, 3 had microcephaly with developmental delay and 2 had macrocephaly with developmental delay. On analyzing data out of 22 infants with developmental delay 50% were male infants and 50% were female infants, among 10 microcephaly 60% were male and 40% were female infants. There was no predilection for sexes as observed in other studies.

53% were delivered by normal vaginal delivery 41 % were delivered by caeserian section, 4% were born by forceps delivery. There was no difference in outcome between the two groups. Similar finding was observed in study conducted by Pisani et al.[33]

Etiology of seizure

The major cause of neonatal seizure in our study was birth asphyxia (33%) , followed by septicemia (27%) , hypoglycemia (20%), and hypocalcemia (8%). The remaining 8% of neonatal seizure is idiopathic. Perinatal asphyxia was predominant cause in most of the studies. In Tekgul et al study 40% of neonatal seizures were due to global cerebral hypoxic ischemia, followed by focal cerebral ischemia 17%, transient metabolic conditions were 3%, and infection 3% , idiopathic causes for neonatal seizure were 17%.[14] In a study by Pisani et al cerebral hypoxic ischemia, intraventricular hemorrhage, and meningitis were predominant causes.[33] In a study done by Arthur et al metabolic disturbances; intracerebral birth injuries and perinatal anoxia, once considered main causes for neonatal seizures, were considerably less frequent.[40] In study conducted by Nunes et al most common etiology was hypoxic ischemic encephalopathy (51%), followed by transient metabolic disturbances (14%), infection (congenital, septicemia, bacterial meningitis – 9%) intraventricular hemorrhage (6%), venous infarct (3%), inborn error of metabolism (2%) and cerebral dysgenesis (2%).[38] In a study by Iype et al multiple causes were accounting for 47.2% of cases of neonatal seizure, 40.5% was due to hypoxic ischemic encephalopathy, hypoglycemia 32.5%.[34]

Our study showed similar etiological profile as other studies, except for Arthur et al.

Type of seizure

Subtle seizure was the most common type of seizure in our study (42%) followed by focal(26%), tonic (19%). Subtle seizure was the most common seizure observed in various studies. In studies by Mizrahi EM et al and Volpe JJ subtle seizures were most common seizures types. In Iype et al 60.7% (82/135) of patients had focal clonic seizures, 14.1% (19/135) had subtle seizures, 21.5% (29/135) had tonic seizures and 3.7% (5/135) had myoclonic seizures.[34] In study by Kim et al subtle seizure accounted for 24%, common type being multifocal clonic (42%).[7] In Tekgul et al common seizure type was clonic seizure (64%), followed by tonic seizure (19%).[14]

Neurodevelopmental outcome

Developmental assessment with Trivandrum Development Screening Chart showed that out of 91 infants, at the end of 1year follow up, adverse neurological outcome was noted in 37 cases ; out of this 37 cases of adverse outcome, 22 had only developmental delay, 10 had isolated microcephaly, 3 had 'microcephaly with developmental delay' and '2 had macrocephaly with developmental delay'. Remaining 54 cases had normal neurological development. Adverse neurological outcome noted in our study was 40% while other studies also showed similar adverse neurological outcome (ie. between 30%- 50%).

Iype et al study shows out of 100 who came for follow up, 32 had developmental delay. Of those with developmental delay, 7 of the babies

followed up had post neonatal epilepsy, 24 had spasticity, 10 had abnormal vision and 5 had defective hearing at four months follow-up. 68 babies were normal at follow up.[34] In a study by Tekgul et al 64 had favourable outcome. and 28% had poor neurological outcome.[(14)]

Arthur et al studied 137 term newborns with neonatal seizure and followed for 4 years. 50% of subjects had normal outcome, 20% died and 30% survived with serious neurological deficit.[40] In a study by Grafinkle et al, 62 term neonatal seizure subjects were followed. A total of 23 (37%) infants had a normal outcome, 34 (55%) survived with 1 or more neurodevelopmental impairments (23 cerebral palsy, 28 global developmental delay, 15 epilepsy, with 18 having combination of two outcome, and 9 all three outcomes), and 5 (8%) died.[37] In a study by Tudehope et al, out of 156 newborns with neonatal seizure over 5 years, 43% had long-term disability.[39] In a study by Ronen et al 45% had normal outcome, 39% had impairment.[35]

Predictors of neurodevelopmental sequelae

Various factors play role as predictors of adverse neurological outcome. Many studies have found constellation of parameters to prognosticate adverse outcome. In our study out of 37 cases of adverse neurological outcome, 37% were due to birth asphyxia, which was statistically not significant. In our study no statistical significance was found between etiology and neurodevelopment outcome. The same conclusion was observed in other studies also. In Iype et al study statistical significance could not be established between etiology and abnormal neurological outcome. Similarly in Nunes et al study no significant statistical

relationship between etiology and the neurodevelopmental outcome was observed.[38] Contrary to the above two studies, in Tekgul et al study the statistical relationship between neonatal seizure etiology and poor outcome was found to be highly significant.[14]

Onset of seizure: in our study early onset of seizure(seizures within 24 hours) showed poor prognosis. Because out of 42 cases of seizures manifesting in < 24 hrs, 72% of subjects had developmental delay, which was statistically significant. Early onset of seizure was poor prognostic factor in other studies also. In Garfinkle et al concluded in his study that seizure occurring less than 24 hours of life is a major determinant of adverse neurological outcome.[37] Volpe JJ proposed that early onset seizure has worst prognosis.[8] Tekgul et al in his study had 64% of neonatal seizure manifesting in less than 24 hours, 20% between 24 to 72 hours, 16% of seizures occurred after 72 hours.[14]

Type of seizure: Type of seizure is an independent risk factor for adverse neurological outcome. But in our study, however no statistical significant association was established between type of seizure and developmental delay. While comparing other studies, some of them have shown that there was no relation between type of seizure and adverse neurological outcome, while some studies have shown there was a relation between etiology and outcome. In a study by Tekgul et al the relationship between the type of neonatal seizure and overall outcome did not achieve statistical significance.[14] In a study by Iype et al clonic seizure was common and no statistical significance was established between seizure type and neurological outcome.[34] But, in a study by Garfinkle, seizure other than focal clonic type had adverse outcome[37] and Tudehope et al observed that tonic seizure

had highest mortality and morbidity.[39] Brunquell et al aso observed in his study that subtle seizure had abnormal neurological outcome.[36]

EEG abnormality: In our study 22 subjects had abnormal EEG record. Among them 7 had mild background abnormality, 15 had moderate to severe abnormal background activity. Out of this 22 cases with abnormal EEG, Developmental delay was observed in 13 subjects , 2 cases had isolated microcephaly, 2 cases had 'microcephaly with developmental delay, and one case had 'macrocephaly with developmental delay'. While 4 cases had normal outcome.

In our study, there was significant association between abnormal EEG and development delay(p value <0.001) which is similar to other studies. Iype et al observed that initial EEG showing predominant spike waves was associated with abnormal neurodevelopment in 50% (4/8) of cases. Sharp waves or a normal EEG were associated with abnormal development in 48% and 22.7% respectively.[34] In Tekgul et al normal EEG record was observed in 21 cases, out of which 4 had unfavourable outcome, 26 EEG records were mild abnormality, 31 were moderate abnormality, 11 were severe abnormality. Association between abnormal EEG with poor neurological outcome was noted in so many studies.[46,47] Garfinkle et al, Ronen et al, Kim et al, Arthur et al, all observed that abnormal EEG record was associated with poor long term neurological outcome.[37,35,6]

Low 5 minute Apgar score : In our study out of 27 newborns who had low Apgar score at 5 minutes of life 9 had developmental delay(33%). Among them 8 subjects had score less than 3/10. Our study's observation was similar to the one conducted by Tudehope et al and Mellits et al.[(39,42)]

SUMMARY

SUMMARY

- A prospective study was conducted at NICU of Institute of Social Paediatrics and NICU of Govt. RSRM hospital to assess the neurodevelopmental sequelae in infants who had neonatal seizure.

- Out of 1856 newborn admission 108 newborn had neonatal seizure, of which 100 participated in the study, 91 infants completed the study, 4 newborns expired during the hospital stay and 5 were lost in follow-up.

- 55% were delivered by spontaneous vaginal delivery, 41 % were born by LSCS , 4% were delivered by forceps and 2% by vacuum extraction.

- 33% of neonatal seizure were due to birth asphyxia, 27 % due to septicemia,

  20 % due to hypoglycemia. In 8% of cases cause was unknown.

- Subtle seizure was the most common seizure(42%), followed by focal seizure(26%), tonic seizure(19%) Mixed type of seizure was observed in 8 % of cases.

- 46% of seizure manifested within 24 hours of life, 34% of cases between 24 to 72 hours of life, 5% of cases occurred after 14 days.

- 20% of hypoglycemic seizure had developmental delay and level of blood glucose did not have significant association with the outcome.

- EEG recorded for 91 cases; out of these 91 cases 22 had abnormal background activity, of which 15 had moderate to severe abnormal background activity, 7 had mild abnormal background activity.

- Family history of seizure was present in 4 newborns among them 2 had developmental delay, though statistical significance was not established.

- Regarding neurodevelopmental outcome, 37 had adverse neurological outcome. Out of this 37 cases 22 had only developmental delay, 10 cases had isolated microcephaly, 3 cases had 'microcephaly with developmental delay' and two cases had macrocephaly.

- The risk factors observed to have adverse outcome were onset of seizures(<24 hours), etiology of seizures, low 5 minute apgar score and abnormal EEG record. .

- 37% of adverse neurological outcome was due to birth asphyxia.

- Low 5 minute apgar score was associated with significant developmental delay.

- EEG abnormality had significant developmental delay. Out of 22 cases with abnormal EEG, Developmental delay was observed in 13 subjects , 2 cases had isolated microcephaly, 2 cases had 'microcephaly with developmental delay, and one case had 'macrocephaly with developmental delay'. While 4 cases had normal outcome.

CONCLUSION

CONCLUSION

From our study it may be concluded that 59% of infants with neonatal seizure had normal development, while 41% had adverse neurological outcome at the end of 1 year follow-up. The risk factors for developmental delay from our study was early onset of seizure, low 5 minute Apgar score and abnormal background EEG.

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ABBREVIATIONS

ABBREVATIONS

ABG	-	Arterial Blood Gas
CT	-	Computed Tomography
DM	-	Diabetes Mellitus
EEG	-	Electro Encephalography
GABA	-	Gama Amino Butyric Acid
HIE	-	Hypoxic Ischemic Encephalopathy
HSC	-	Health SubCentre
HSV	-	Herpes Simplex Virus
IEM	-	Inborn Error of Metabolism
IVH	-	Intraventricular Hemorrhage
MDI	-	Mental Development Index
MRI	-	Magnetic Resonance Imaging
NCCP	-	National Collaborative Perinatal Project
NS	-	Neonatal Stroke
PHC	-	Primary Health Centre
PIH	-	Pregnancy Induced Hypertension
PROM	-	Premature Rupture Of Membrane
TDSC	-	Trivandrum Development Screening Chart

ANNEXURES

PROFORMA

CGC NO:

NAME:

AGE:

SEX:

ADDRESS:

TYPES OF SEIZURES: subtle/focal/tonic/myoclonic/mixed :S1/S2/S3/S4

Family h/o seizures: yes/no

Family h/o developmental delay: yes/no

ANTENATAL HISTORY :

- h/o fever with rashes: yes/no
- h/o maternal fever during labour/ <2 weeks before labour: yes/no
- h/o maternal GDM: yes/no
- h/o p/v >3 during labour: yes/no
- H/O PIH: yes/no

BIRTH HISTORY:

- mode of delivery : vaginal delivery / LSCS/forceps/vaccum: M1/M2/M3/M4
- apgar score : 1min _/5min_
- baby resuscitated: yes/no
- gestational age:
- birth weight:2.5-3kg /3-4kg />4kg :B1/B2/B3
- liquor: clear/ meconium stained/ foul smelling: L1/L2/L3
- DOB:
- Place of delivery:RSRM/CORP HOSPITAL/PHC/HSC/PRIVATE HOSPITAL : PD1/PD2/PD3/PD4/PD5

POSTNATAL HISTORY:

- day of onset of seizure: <24 hrs/ 24-72hrs/ >72hrs: D1/D2/D3
- no of episodes of seizure:
- DATE OF ONSET OF SEIZURE:

- DATE OF DEATH:
- Etiology of seizure:

EXAMINATION:

- alert: yes/no
- active: yes/no
- pallor: yes/no
- febrile : yes/no
- cyanosis: yes/no
- dysmorphic facies: yes/no
- neurocutaneous markers: yes/no
- CVS:
- RS
- P/A:
- CNS:
  - AF
  - Bulk- wasting: yes/no
  - Tone: increased/decreased/normal: T1/T2/T3
  - Reflexes : normal/exaggerated/absent: R1/R2/R3
  - Power : grades 1/2/3/4/5
- Plantar : extensor/ flexor/no response :P1/P2/P3

ANTHROPOMETRY:

anthropometry	birth	3m	6m	9m	12m
Wt (kg)					
Length (cm)					
HC (cm)					
CC (cm)					

INVESTIGATION:

- EEG: normal/abnormal: E1/E2
- CT BRAIN: NORMAL/ ABNORMAL: C1/C2
- Plasma sugar: <20mg/ 21-35mg/ 36-45mg/ >45mg: BS1/BS2/BS3/BS4
- Serum calcium.: LOW/ NORMAL: SC1/SC2
- Lumbar puncture: MENINGITIS/ NO MENINGITIS: LP1/LP2
- blood culture: POSITIVE/NEGATIVE: BC1/BC2
- Urine for metabolic screening: POSITIVE/NEGATIVE: MS1/MS2
- CRP: POSITIVE/NEGATIVE: ½

KEY TO MASTER CHART

1) Sex of the baby:

1- male

2- female

2) Place of delivery:

1- Govt. RSRM Hospital

2- corporation hospital

3- PHC

4- Private hospital

5- HSC

3) Mode of delivery :

1- spontaneous vaginal delivery

2- LSCS

3- forceps delivery

4- vacuum extraction.

4) Type of seizure :

1- subtle

2- tonic

3- focal

4- myoclonic

5- mixed

5) Onset of seizure:

1- <24 hours

2- 24 to 72 hours

3- >72 hours

6) Etiology:

1- birth asphyxia

2- septicemia

3- hypoglycemia

4- hypocalcemia

5- IVH

6- Neonatal Stroke

7- Inborn error of metabolism

8- idiopathic

7) Hypoglycemia blood glucose value:

1- <20 mg%

2- 20mg% - 35mg%

3- 36 mg% to 45 mg%

4- >45 mg

8) EEG RECORD:

1- normal

2- abnormal

9) Antenatal Complication:

1- PIH

2-DM

3- maternal fever

4- PROM

5- no complications

10) Birth weight:

1- 2.5 kg to 3 kg

2- 3 kg to 4 kg

3- >4kg

11) Family history of seizure:

1- no

2-yes

12) Apgar score at 1 minute:

1 – less than 3

2 – score 3-8

3- more than 8

14) Apgar at 5 minute:

1 – less than 3

2- score 3 to 8

3 – more than 8

15) Neurodevelopmental delay:

1- no

2- yes

16) Microcephaly :

1- no

2-yes

17) Microcephaly with developmental delay :

1- no

2- yes

18)Macrocephaly:

1- no

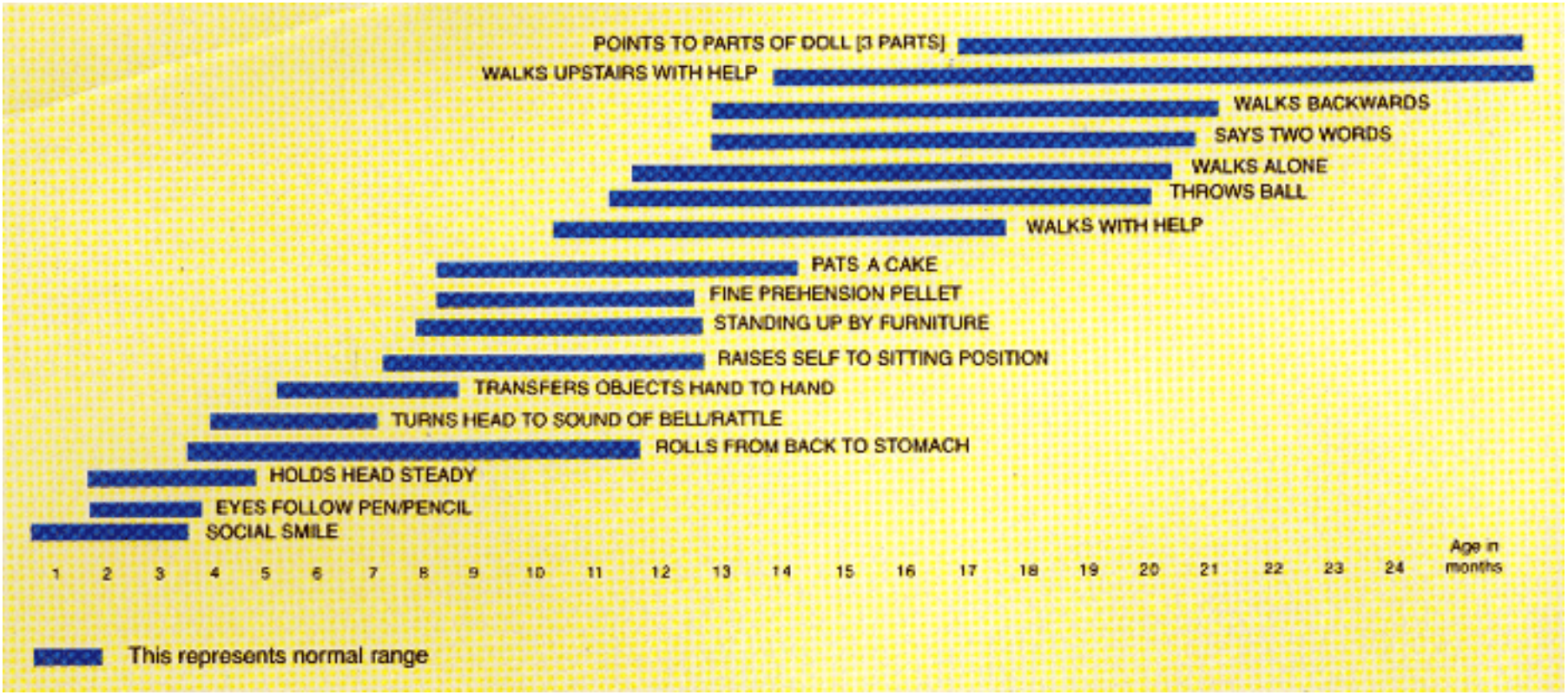
2- yes

19)Macrocephaly with developmental delay:

1- no

2- yes

TRIVANDRUM DEVELOPMENT SCREENING CHART

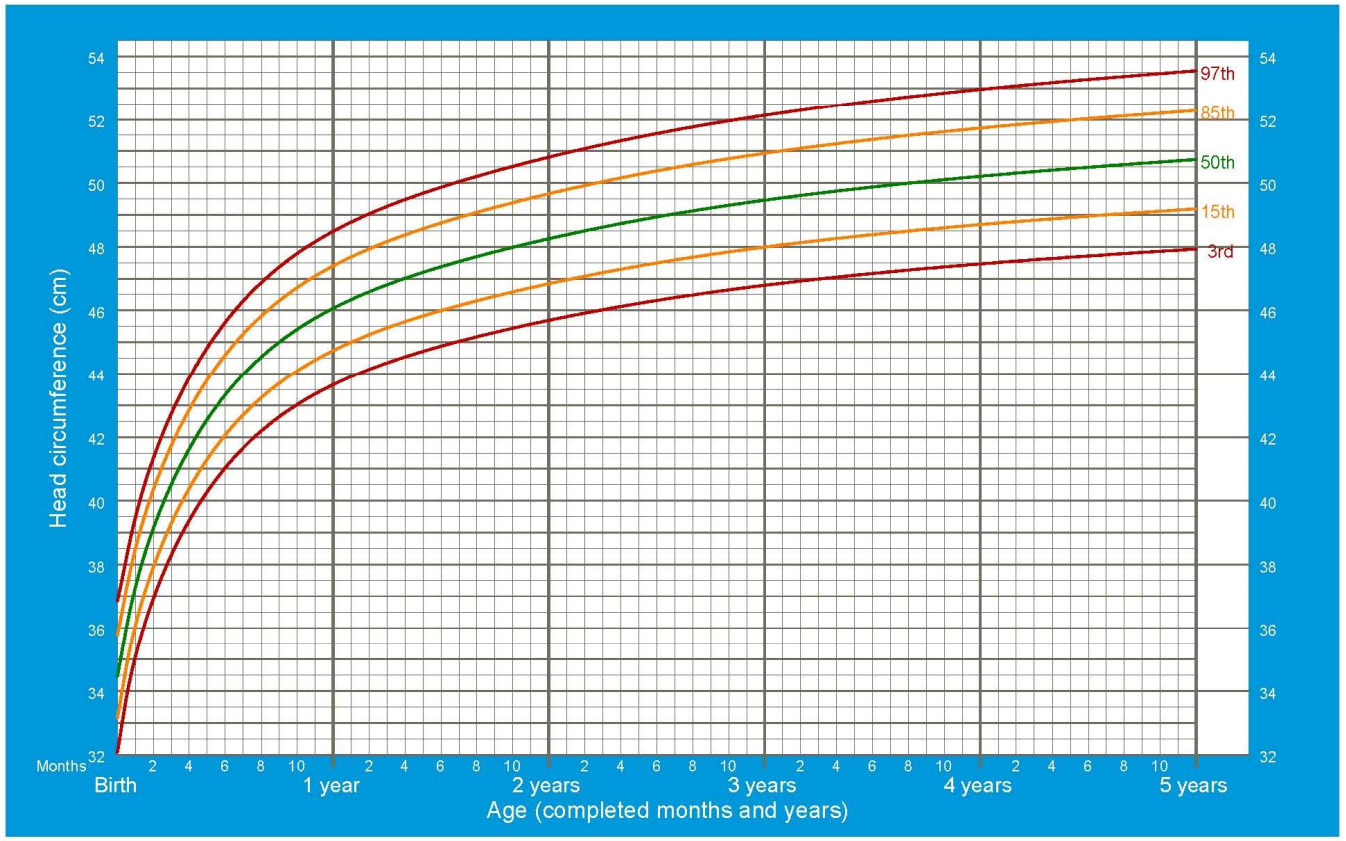


IX.

Head circumference-for-age BOYS

Birth to 5 years (percentiles)

World Health Organization

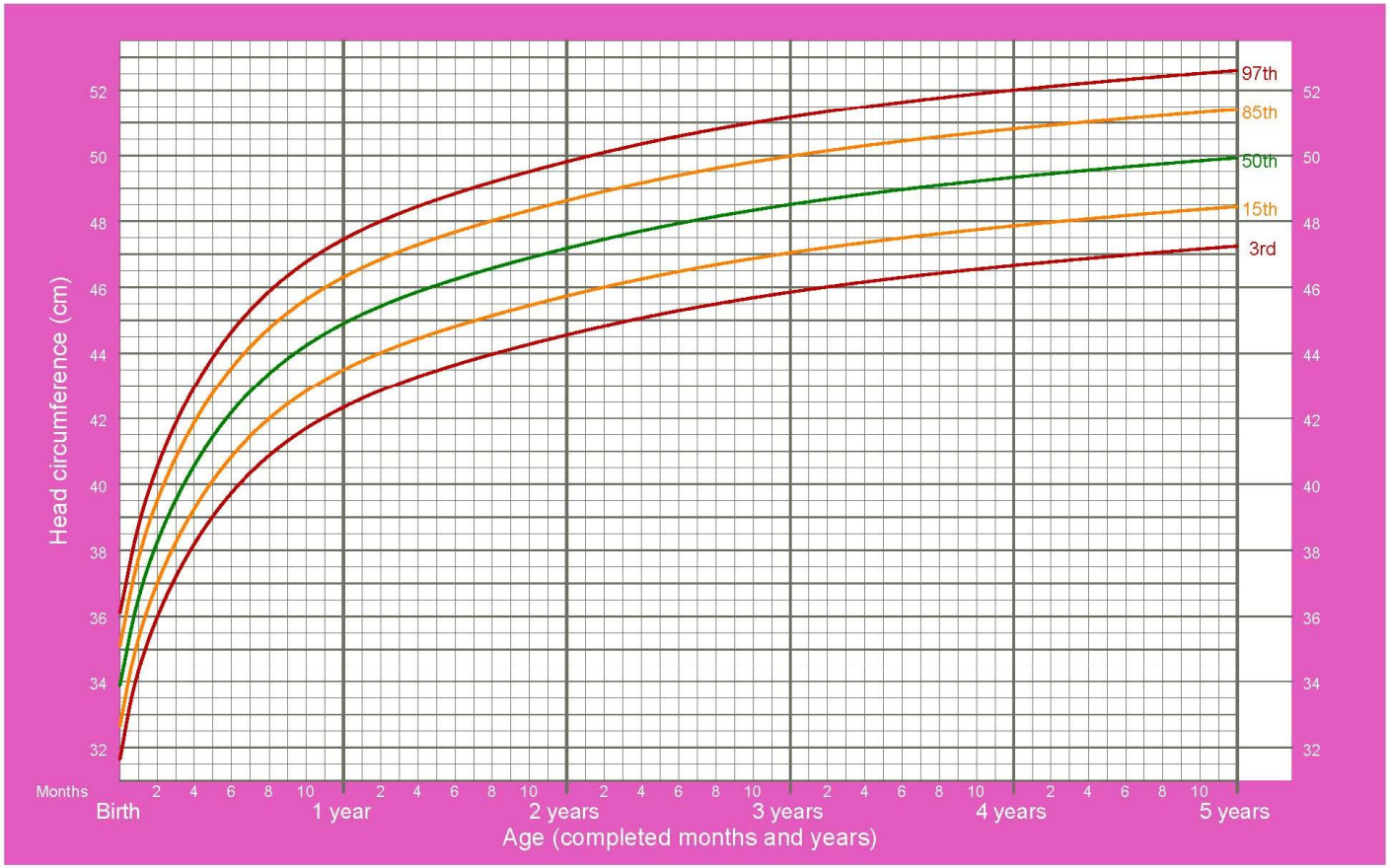


WHO Child Growth Standards

Head circumference-for-age GIRLS

World Health Organization

Birth to 5 years (percentiles)



WHO Child Growth Standards

Name	sex	place of delivery	mode of delivery	type of seizure	onset	etiology	hypoglycemia	EEG	antenatal complication	birth weight	family history	APGAR SCORE 1 MIN	APGAR SCORE 5 MIN	neuro developmental delay	MICROCEPHALY	developemental delay+ microcephaly	MACROCEPHALY	macrocephaly+ developemental delay
B/O SAROJA	1	1	1	1	1	1	4	1	1	1	1	1	1	1	2	1	1	1
B/O RANI	1	1	1	1	2	1	4	1	2	1	1	1	2	1	1	1	1	1
B/O RAMYA	2	2	1	2	2	2	4	1	4	1	2	3	3	1	1	1	1	1
B/O PADMA	1	1	1	5	1	1	4	2	5	1	1	1	3	1	1	1	1	1
B/O KALAIMANI	1	1	2	2	2	2	4	1	4	1	1	3	3	1	1	1	1	1
B/O VIJAYA	2	1	1	2	1	4	4	1	3	1	1	3	3	1	1	1	1	1
B/O AROKIAMARY	1	1	1	1	1	3	1	1	5	1	1	3	3	2	1	1	1	1
B/O LAVANYA	2	2	2	1	1	4	4	1	3	1	1	3	3	1	1	1	1	1
B/O THAMIZHSELVI	1	1	1	3	2	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O FATHIMA	2	3	1	1	1	3	3	1	5	1	1	3	3	1	1	1	1	1
B/O VALLIAMMAL	1	1	2	1	1	1	4	2	4	1	1	1	1	2	1	1	1	1
B/O MUMTAJ	2	1	1	1	2	2	4	1	5	1	1	3	3	1	1	1	1	1
B/O PUSHPARANI	2	1	1	3	1	3	3	1	5	1	1	3	3	1	1	1	1	1
B/O SELVI	1	2	1	1	2	2	4	1	5	1	2	3	3	1	1	1	1	1
B/O GEETHA	2	1	2	1	3	2	4	1	2	1	1	3	3	1	1	1	1	1
B/O FARZANA	2	4	1	2	1	1	4	1	5	1	1	2	3	1	1	1	1	1
B/O SAHAYAMARY	1	1	1	3	1	3	3	1	5	1	1	3	3	1	1	1	1	1
B/O SNEHA	1	5	2	2	1	4	4	1	4	1	1	3	3	1	2	1	1	1
B/O NIRMALA	2	1	2	2	2	4	4	1	1	1	1	3	3	1	2	1	1	1
B/O KANIMOZHI	1	1	1	1	1	1	4	2	5	1	1	1	1	2	1	1	1	1

B/O TAMHIZHARASI	1	1	2	3	2	2	4	1	1	1	1	3	3	1	1	1	1	1
B/O MANJULA	2	1	2	1	1	3	1	1	2	3	1	3	3	1	1	1	1	1
B/O THENMOZHI	2	1	2	3	3	2	4	1	5	1	1	3	3	1	1	1	1	1
B/O RADHIKA	1	2	2	3	1	3	3	1	5	1	1	3	3	2	1	1	1	1
B/O SIVAPRIYA	1	1	1	1	2	1	4	1	1	1	1	1	1	2	1	1	1	1
B/O MADHAMMAL	1	1	1	3	1	1	4	1	5	1	1	1	2	1	2	1	1	1
B/O PRIYADHARSHINI	2	1	1	1	1	3	1	1	5	1	1	3	3	1	1	1	1	1
B/O PRIYA	2	2	2	1	1	2	4	2	5	1	1	3	3	2	1	1	1	1
B/O YASODHA	1	1	3	2	1	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O MUNIAMMA	1	1	2	4	3	2	4	2	5	1	1	3	3	1	1	2	1	1
B/O VALLI	2	1	2	2	3	2	4	1	5	1	1	3	3	1	1	1	1	1
B/O ARULMARY	2	3	1	1	1	1	4	1	4	1	1	1	2	1	2	1	1	1
B/O DEVIKA	1	1	1	1	2	3	2	1	5	1	1	3	3	1	2	1	1	1
B/O SAMUNDEESWARI	1	1	1	3	1	1	4	2	3	1	1	1	1	2	1	1	1	1
B/O KALPANA	1	1	1	1	1	8	4	1	5	1	1	2	3	1	1	1	1	1
B/O SHOBANA	2	1	1	5	2	1	4	2	5	1	1	1	2	1	1	1	1	1
B/O SUMITHRA	2	1	1	3	2	2	4	2	5	1	1	3	3	1	1	1	1	1
B/O JANAKI	2	5	2	1	1	1	4	1	5	1	1	2	2	1	2	1	1	1
B/O JAYAROOPA	2	1	2	1	3	2	4	1	1	1	1	3	3	1	1	1	1	1
B/O AMUDHA	1	1	1	1	1	3	3	1	5	1	1	3	3	1	1	1	1	1
B/O SUJATHA	2	1	2	2	3	2	4	2	5	1	1	3	3	2	1	1	1	1
B/O BANUPRIYA	1	1	1	1	1	1	4	1	5	1	1	1	1	2	1	1	1	1
B/O SNEHA	2	1	1	4	2	1	4	2	5	1	1	1	1	1	1	2	1	1
B/O SARASWATHI	2	3	2	3	3	2	4	1	1	1	1	3	3	1	1	1	1	1

B/O SUBASHINI	1	1	2	1	2	2	4	2	5	1	1	3	3	1	2	1	1	1
B/O DEEPA	2	1	1	2	3	2	4	1	5	1	1	3	3	1	1	1	1	1
B/O SIVAGAMI	2	1	2	4	1	8	4	2	1	1	1	3	3	2	1	1	1	1
B/O KAVITHA	1	2	1	1	1	8	4	1	5	1	1	3	3	1	1	1	1	1
B/O SANGEETHA	2	1	2	1	2	2	4	1	5	1	2	3	3	2	1	1	1	1
B/O VIMALATHA	1	1	2	2	1	1	4	1	5	1	1	1	1	1	1	1	1	1
B/O SINDHU	1	1	2	1	2	3	1	1	5	1	1	3	3	1	1	1	1	1
B/O VANAJA	2	1	2	1	1	8	4	2	5	1	1	3	3	2	1	1	1	1
B/O PARVEEN BANU	1	2	1	3	2	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O CHITHRA	1	1	2	2	1	3	2	1	2	3	1	3	3	2	1	1	1	1
B/O SARALA	1	2	2	3	2	3	3	1	5	1	1	3	3	1	1	1	1	1
B/O MENAKA	2	1	2	5	3	2	4	2	5	1	1	3	3	2	1	1	1	1
B/O RUPA	1	1	1	2	1	1	4	2	5	1	1	1	1	2	1	1	1	1
B/O MALARVIZHI	2	2	3	1	2	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O POONGOTHAI	1	1	2	3	3	2	4	2	5	1	1	3	3	1	1	1	1	2
B/O GEETHARANI	2	1	2	1	1	2	4	2	1	1	1	3	3	2	1	1	1	1
B/O JAYALAKSHMI	1	2	1	2	3	4	4	1	5	1	1	3	3	1	1	1	1	1
B/O SATHYA	2	1	1	1	1	1	4	2	5	1	1	1	1	2	1	1	1	1
B/O BHUVANESWARI	1	1	2	3	2	4	4	1	1	1	1	3	3	1	1	1	1	1
B/O JOTHI	2	5	1	2	3	4	4	1	5	1	1	3	3	1	1	2	1	1
B/O VIJAYAPRIYA	1	1	1	1	2	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O VIMALA	2	2	1	4	2	1	4	2	4	1	1	1	1	2	1	1	1	1
B/O SIVARANJANI	1	1	1	1	1	8	4	1	5	1	1	3	3	1	1	1	1	1

B/O ESWARI	1	1	1	3	2	1	4	1	5	1	1	2	3	1	1	1	1	1
B/O ANURADHA	1	2	2	1	1	3	2	1	5	1	1	3	3	1	1	1	1	1
B/O GAYATHRI	2	1	1	5	3	3	1	1	5	1	1	3	3	2	1	1	1	1
B/O LOKESHWARI	1	1	1	2	1	3	2	1	2	2	1	3	3	1	1	1	1	1
B/O YASMIN	1	4	1	3	2	2	4	1	3	1	1	3	3	1	1	1	1	2
B/O IRFANA	2	3	1	5	3	8	4	1	5	1	1	3	3	1	2	1	1	1
B/O JAYABHARATHI	1	1	1	2	1	3	2	1	5	1	1	3	3	1	1	1	1	1
B/O ANBUMALAR	2	2	2	3	2	2	4	1	1	1	1	3	3	1	1	1	1	1
B/O MOHANAMBAL	2	1	2	2	1	1	4	1	1	1	1	2	2	1	1	1	1	1
B/O POONKODI	2	1	2	3	2	8	4	1	2	1	2	3	3	1	1	1	1	1
B/O KUMARI	2	2	1	2	3	3	2	1	5	1	1	3	3	1	1	1	1	1
B/O RAMA	2	1	1	1	1	1	4	2	5	1	2	1	1	2	1	1	1	1
B/O SHANTHI	2	1	1	3	2	1	4	1	1	1	1	1	2	1	1	1	1	1
B/O HEPSIBA	2	1	2	1	1	2	4	1	3	1	1	2	3	1	1	1	1	1
B/O RAJESWARI	2	1	2	3	3	3	3	1	2	2	1	3	3	1	1	1	1	1
B/O ARUNA	1	5	1	5	3	2	4	2	5	1	1	3	3	1	2	1	1	1
B/O GANDHIMATHI	1	2	2	3	1	8	4	1	5	1	1	3	3	2	1	1	1	1
B/O ANITHA	2	1	1	5	2	1	4	2	5	1	1	1	2	1	1	1	1	1
B/O ANANDHI	1	1	1	1	3	3	2	1	5	1	1	3	3	1	1	1	1	1
B/O SASIREKHA	1	1	1	1	1	1	4	1	4	1	1	1	2	1	1	1	1	1
B/O GIRIJA	2	2	1	1	2	1	4	1	5	1	1	1	2	1	1	1	1	1
B/O JANANI	1	1	2	3	1	4	4	1	2	1	1	3	3	2	1	1	1	1
B/O MALARVIZHI	2	1	2	1	3	2	4	1	1	1	1	3	3	1	1	1	1	1
B/O NITHYA	1	1	2	5	2	3	1	1	5	1	2	3	3	1	1	1	1	1